CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210795Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA, 505(b)(1)
Application Number(s)	210795
Priority or Standard	Priority
Submit Date(s)	11/22/2017
Received Date(s)	11/22/2017
PDUFA Goal Date	07/22/2018
Division/Office	DAIP/OAP
Established Name	Tafenoquine
(Proposed) Trade Name	KRINTAFEL
Pharmacologic Class	Antimalarial
Applicant	GlaxoSmithKline Intellectual Property Development Ltd. England
Formulation(s)	Oral Tablet
Dosing Regimen	Two 150 mg tablets, single-dose
Applicant Proposed Indication(s)/Population(s)	Radical cure (prevention of relapse) of *P. vivax* malaria in patients 16 years of age and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Radical cure (prevention of relapse) of *P. vivax* malaria in patients 16 years of age and older

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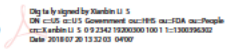
	Signature: Xianbin Li -S 			
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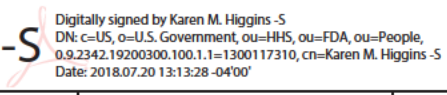
	Signature: Karen M. Higgins -S 			
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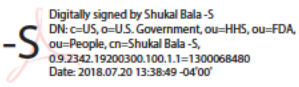
	Signature: Shukal Bala -S 			
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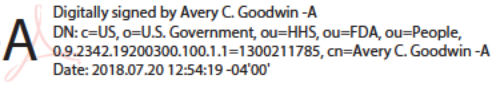
	Signature: Avery C. Goodwin -A 			

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

Glossary

AC advisory committee
ADME absorption, distribution, metabolism, excretion
ADR adverse drug reaction
AE adverse event
AESI adverse events of special interest
BPCA Best Pharmaceuticals for Children Act
CDC Center for Disease Control and Prevention
CDER Center for Drug Evaluation and Research
CDRH Center for Devices and Radiological Health
CDTL Cross-Discipline Team Leader
CFR Code of Federal Regulations
CI Confidence interval
CMC chemistry, manufacturing, and controls
CQ chloroquine
CRF case report form
CRO contract research organization
CRT clinical review template
CSR clinical study report
DAIP Division of Anti-Infective Products
DMC data monitoring committee
DPV Division of Pharmacovigilance
ECG electrocardiogram
eCTD electronic common technical document
FDA Food and Drug Administration
GCP good clinical practice
GLP good laboratory practice
ICH International Conference on Harmonization
IND Investigational New Drug
ISE integrated summary of effectiveness
ISS integrated summary of safety
ITT intent-to-treat
ITT-E intent-to-treat exposed
MedDRA Medical Dictionary for Regulatory Activities
MQ mefloquine
mITT modified intent to treat
NDA new drug application
NME new molecular entity
OPQ Office of Pharmaceutical Quality
OSE Office of Surveillance and Epidemiology

OSI Office of Scientific Investigation
PD pharmacodynamics
PK pharmacokinetics
PMC postmarketing commitment
PMR postmarketing requirement
PP per protocol
PPI patient package insert
PQ primaquine
PREA Pediatric Research Equity Act
PRO patient reported outcome
REMS risk evaluation and mitigation strategy
SAE serious adverse event
SD Standard Deviation
TEAE treatment emergent adverse event
TQ tafenoquine
USPI US prescribing information
WHO World Health Organization

1 Executive Summary Office Level Concurrence

1.1. Product Introduction

Tafenoquine (TQ), KRINTAFEL, is an 8-aminoquinoline antimalarial drug. In NDA 210795, TQ is being developed as a therapeutic for radical cure of *Plasmodium vivax* malaria because of its activity against the dormant liver stage, hypnozoite of *P. vivax*. As TQ has slow clearance of the blood stage, co-administration with another faster acting blood schizonticide (e.g. chloroquine (CQ) for 3 days) is required for treatment of *P. vivax* malaria as this combination targets both blood and liver hypnozoite stages of infection.

The proposed indication is radical cure (prevention of relapse) of *P. vivax* malaria in patients 16 years of age and older. The proposed dose is TQ 300 mg as a single dose, i.e. two 150 mg tablets, administered on Day 1 or Day 2 of CQ therapy.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support approval of TQ administered concurrently with CQ for the radical cure of *P. vivax* malaria. In two adequate and well-controlled trials, recurrence of *P. vivax* malaria was significantly lower in subjects who received TQ 300 mg + CQ compared to CQ alone. In a placebo-controlled phase 3 clinical trial, the odds ratio of the risk of recurrence with TQ +CQ versus placebo + CQ was 0.24 (95% CI, 0.15-0.38), $p<0.001$. In a dose-escalation trial, the TQ 300 mg +CQ group had a statistically significant higher rate of recurrence-free efficacy at 6 months compared with the placebo + CQ (84% versus 39%, with a difference of 45% and 95% CI [29%, 61%]). Supportive evidence was provided from a randomized active-control phase 3 safety trial, where the recurrence-free efficacy proportion was comparable between the two treatment groups, TQ + CQ versus Primaquine (PQ) + CQ. See sections 7.2, 7.3, and 7.4 for details of the efficacy analyses.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In NDA 210795, TQ is being developed as a therapeutic for the radical cure of *P. vivax* malaria because of its activity against the dormant liver stage, hypnozoite, of *P. vivax*. Because TQ has a terminal half-life of approximately 15 days, a single-dose of TQ is considered adequate to treat the hypnozoites of *P. vivax.* TQ has slow clearance of the erythrocytic stage; therefore, co-administration with another faster acting blood schizonticide (e.g. CQ x 3 days) is required for the treatment of *P. vivax* malaria as this combination targets both blood and liver stages of the infection. The key studies in NDA 210-795 include a phase 2b trial (TAF112582-part 1) and two phase 3 trials (TAF112582-part 2 and TAF116564) to support the efficacy and safety of TQ for the radical cure of *P. vivax* malaria in for patients 16 years of age and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection.

In study TAF112582-Part 1, the primary endpoint, i.e. recurrence-free efficacy rates at six months post-dose, was statistically significantly better in the TQ 300 mg group (84%), compared to the placebo group (39%) with a difference of 45% and 95% CI (29%, 61%). In Study TAF112582- Part 2, a statistically significant difference in the recurrence-free efficacy rate at 6 months post-dose was observed for TQ+CQ (60%) compared with CQ alone (26%). The odds ratio of the risk of recurrence with TQ +CQ versus placebo plus CQ was 0.24 (95% CI, 0.15-0.38), p<0.001. The risk of recurrence of *P. vivax* malaria for TQ +CQ was reduced by 75.9%, 95% CI (61.8%, 84.8%); p<0.001 compared with CQ + placebo. Both parts of TAF112582 included an arm with PQ 15 mg daily for 14 days + CQ as a benchmark (with 6-month recurrence-free efficacy rates of 68% and 64% for Part 1 and Part 2, respectively). Supportive evidence was provided from Study TAF116564, a randomized active-control phase 3 safety trial, where the recurrence-free efficacy proportion was comparable between the two treatment groups, TQ + CQ versus PQ + CQ.

In general, TQ 300 mg single-dose was well-tolerated. A total of 810 patients in a clinical database of greater than 4000 were exposed to a single dose of TQ 300 mg, the proposed dosing regimen. In the clinical trials, asymptomatic reversible decreases in hemoglobin were observed and the proportions of subjects with hemoglobin decreases were higher in the TQ+CQ group compared with the CQ alone group in G6PD normal individuals. These differences were not considered to be clinically significant, because few subjects had hemoglobin decreases that fell to below the lower limit of normal and all recovered without medical intervention such as blood transfusion. Similar to PQ, the main safety risk of TQ is hemolytic anemia in subjects with G6PD deficiency. TQ must not be prescribed to subjects with G6PD deficiency or those with unknown G6PD status. Methemoglobinemia, a class effect for the 8-aminoquinolines, was observed more frequently in the PQ+CQ group compared to the TQ+CQ treatment group. Nausea, vomiting, dizziness, headache, pruritus, insomnia, upper abdominal pain, and diarrhea occurred in ≥3% of patients treated with TQ+CQ. Pruritus was deemed to be related to CQ. There was no evidence that TQ exacerbates the

adverse effects of CQ. Psychiatric adverse reactions such as anxiety and depressed mood were uncommon and occurred in <1% of patients. Psychosis was reported in two (<1%) patients with a history of psychiatric illness, psychosis and schizophrenia. Depressed mood occurred in two subjects, one in a patient with a previous history of depression, another in a patient with no previous psychiatric history (episode lasted 3 days and resolved spontaneously). In a thorough QT study, TQ had no clinically significant effect on QT interval. Ocular toxicity was not observed in a dedicated ophthalmologic safety study.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• *P. vivax* malaria is a serious infectious disease. • Significant morbidity is related to the potential for relapsing disease.	
Current Treatment Options	• PQ is the only approved treatment option for radical cure (prevention of relapse) of *P. vivax* malaria. Compliance is low with the 7 to 14-day course of PQ as documented in published literature.	A single-dose of TQ 300 mg has the potential to improve compliance and clinical outcomes in patients with *P. vivax* malaria.
Benefit	• A statistically significant difference in the recurrence-free efficacy rate at 6 months was observed for TQ+CQ (60%) compared with CQ alone (26%). The odds ratio of the risk of recurrence with TQ +CQ versus placebo plus CQ was 0.24 (95% CI, 0.15-0.38). • In a dose-ranging trial, a statistically significant difference in the recurrence-free efficacy rate at 6 months was observed for TQ+CQ group (84%) compared with CQ alone group (39%), difference of 45%, 95% CI [29%, 61%]. • Efficacy data from an additional clinical trial comparing TQ +CQ to PQ +CQ supported the efficacy of TQ for radical cure of P. vivax malaria.	• The clinical trials provide substantial evidence of effectiveness for TQ 300 mg single-dose given with CQ for 3 days for the radical cure of *P. vivax* as compared to CQ alone. • Eliminating *P. vivax* hypnozoites decreases morbidity associated with relapse and has the potential to reduce transmission of *P. vivax* in the community.
Risk	• TQ causes hemolysis, hemolytic anemia, and methemoglobinemia in patients with G6PD deficiency. • TQ is associated with reversible decline in hemoglobin and asymptomatic methemoglobinemia in G6PD normal subjects.	• TQ is contraindicated in patients with G6PD deficiency or unknown G6PD status. Monitoring for signs and symptoms of hemolysis should be performed. Patients who experience adverse

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• TQ single-dose has a long half-life of ~ 15 days and adverse reactions, when they occur, may be prolonged or occur late. • TQ may cause hemolytic anemia in a G6PD deficient fetus and G6PD deficient breast-fed infant. • The are no studies of TQ in pregnant or lactating women. • TQ cannot be used to treat acute *P. vivax* malaria as it has slow activity against the erythrocytic stage.	reactions to TQ should be monitored for persistence of these reactions because of the drug's 15-day terminal half-life. • TQ should not be used during pregnancy or in lactating woman whose infant's G6PD status is deficient or unknown. • Labeling includes warnings regarding risk of hemolytic anemia in G6PD deficient individuals, risk of decline in hemoglobin in G6PD normal individuals, use in pregnant or lactating women, risk of hypersensitivity and psychiatric reactions in patients with history of psychiatric illness. • Labeling includes a limitation of use stating that TQ is not indicated for the treatment of acute *P. vivax* malaria. • Labeling also includes patient information describing the adverse reactions.
Risk Management	• TQ is a single-dose therapy for *P. vivax* malaria and a risk evaluation and mitigation strategy is not applicable.	• Testing for G6PD enzyme activity must be performed before TQ use to avoid risk of hemolytic anemia. • The Applicant will be monitoring for the adverse reactions of hemolysis, hypersensitivity, and psychiatric reactions in an active surveillance study as a post-market requirement.

2 Therapeutic Context

2.1. Analysis of Condition

Of the non-falciparum species, *P. vivax* has the greatest geographic range and burden of disease, and worldwide estimates of *P. vivax* infections range between 130 and 390 million (~50% cases of malaria). Approximately 2.5 billion people are at risk of infection. *P. vivax* malaria causes significant morbidity much of which is attributable to the chronic relapsing nature of the infection.[1,2] The burden of *P. vivax* malaria exists in Southeast Asia, South America, and Africa. The CDC received reports of 1,724 confirmed malaria cases, including one congenital case and two cryptic cases, with onset of symptoms in 2014 among persons in the United States. *Plasmodium falciparum, P. vivax, P. ovale,* and *P. malariae* infections were identified in 66.1%, 13.3%, 5.2%, and 2.7% of cases, respectively. The US has approximately 200 imported cases of *P. vivax* annually.[3]

Unlike *P. falciparum, P. vivax* has a liver hypnozoite stage in its life cycle, which allows the infection to relapse days, weeks, or months following apparently effective treatment of the initial infection. Relapse of malaria may occur in the setting of infection with *P. vivax* or *P. ovale* infection. Relapsing infection drives further episodes of illness and hampers elimination efforts. CQ or mefloquine (MQ) used for CQ-resistant strains are commonly used for treatment of the blood (erythrocytic) forms for non-falciparum malaria species such as *P. vivax*. Neither of these drugs have activity against liver hypnozoites *of P. vivax*. For more than 60 years, PQ is the only licensed drug for eradicating (radical cure) *P. vivax* hypnozoites and, therefore, preventing relapses of *P. vivax* malaria.

P. vivax malaria is a serious infection and the severity of disease has been underestimated.[4] Common symptoms and signs of malaria may include fever, chills, malaise, fatigue, shortness of breath, diaphoresis, headache, cough, nausea, vomiting, abdominal pain, diarrhea, arthralgia, and myalgia. Physical findings may include tachycardia, jaundice, splenomegaly and/or hepatomegaly. The mortality rate for *P. vivax* infection is generally low, although one report of 36 cases from Indonesian New Guinea (Papua) noted a death rate of 25 percent.[5] Splenic rupture is a rare complication of acute *P. vivax* malaria and approximately 150 cases have been

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[4] Kochar DK, Saxena V, Singh N, et al. *Plasmodium vivax* malaria. Emerg Infect Dis. 2005;11(1):132
[5] Barcus MJ, Basri H, Picarima H, et al. Demographic risk factors for severe and fatal vivax and falciparum malaria among hospital admissions in northeastern Indonesian Papua. Am J Trop Med Hyg. 2007;77(5):984

described.[6,7] Other severe and less common manifestations of *P. vivax* malaria include, acute respiratory distress syndrome, profound anemia, disseminated intravascular coagulation, renal failure, shock, and cerebral malaria. [8,9,10] Vivax malaria was associated with increased morbidity and mortality in early infancy[11] in Indonesian New Guinea (Papua) and carried an elevated risk of miscarriage in the first trimester in women with acute vivax malaria in Thailand.[10]
P. vivax malaria is diagnosed by blood smear, which remains the gold standard for laboratory confirmation of malaria.

2.2. Analysis of Current Treatment Options

The current recommended treatment regimen for the treatment of *P. vivax* malaria includes a schizontocidal antimalarial, usually CQ, combined with a 14-day course of PQ. TQ has slow clearance of blood stage; therefore, co-administration with another faster acting blood schizonticide (CQ x 3 days) is required for treatment of *P. vivax* malaria as this combination targets both blood and liver stages of infection. CQ-resistant strains of *P. vivax* are reported in a small number of countries such as Indonesian New Guinea (Papua).

The only available drug that has activity against the liver hypnozoites of *P. vivax* and *P. ovale* is PQ, an 8-aminoquinoline antimalarial drug which was approved for the radical cure of *P. vivax* malaria by the FDA in 1952. The FDA approved dose is 15 mg daily for 14 days. In practice, PQ is dosed either at 15 mg or 30 mg daily for 7 to 14 days. PQ is associated with hemolysis in individuals with G6PD deficiency and methemoglobinemia.

Clinical reviewer's comment: In clinical practice, non-compliance with the 14-day course of PQ is common. Douglas et al., reported that PQ is substantially less effective in preventing relapse of vivax malaria in clinical practice than is predicted by efficacy trials and that this is likely the consequence of incomplete adherence to treatment. In their study based on hospital surveillance data, the risk of re-presenting with vivax malaria was 37.2% (95% CI 35.6%–38.8%) in patients in Southern Papua who were not prescribed PQ compared to 31.6% (95% CI 30.9%–32.3%) in those who self-administered either a low or high dose of PQ

[6] Gockel HR, Heidemann J, Lorenz D, et al. Spontaneous splenic rupture, in tertian malaria. Infection. 2006;34(1):43.
[7] Jiménez BC, Navarro M, Huerga H, et al. Spontaneous splenic rupture due to Plasmodium vivax in a traveler: case report and review. J Travel Med. 2007;14(3):188.
[8] Tjitra E, Anstey NM, Sugiarto P, et al. Multidrug-resistant Plasmodium vivax associated with severe and fatal malaria: a prospective study in Papua, Indonesia. PLoS Med. 2008;5(6):e128.
[9] Lomar AV, Vidal JE, Lomar FP, et al. Acute respiratory distress syndrome due to vivax malaria: case report and literature review. Braz J Infect Dis. 2005;9(5):425.
[10] McGready R, Lee SJ, Wiladphaingern J, et al. Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: a population-based study. Lancet Infect Dis. 2012;12(5):388.
[11] Poespoprodjo JR, Fobia W, Kenangalem E, et al. Vivax malaria: a major cause of morbidity in early infancy. Clin Infect Dis. 2009;48(12):1704.

(adjusted Hazard Ratio, AHR = 0.90 [95%CI 0.86–0.95, p < 0.001]). [12] *Several publications report that patients are less likely to take PQ once their symptoms have abated and adherence to the full 14-day course is often low.*[13,14,15,16] *Takeuchi reported that the relapse rate in vivax malaria patients who received DOT with PQ was 3% whereas the relapse rate in patients who self-administered PQ was 11%.* [15] *Similar findings were reported from a study in Ethiopia, where relapse rates were higher with unsupervised PQ compared to PQ administered under supervision.*[17] *Adherence was reported to be low (60%) even with a shorter 7-day course of PQ offered for free.*[18]

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Tafenoquine is not marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 1. Presubmission/Submission Regulatory History

Date	Key Discussion Points
30 January 2008	IND 101471 opened
24 March 2010 Type C Meeting	Agreement on a combined Phase 2b TAF112582 Part 1 and Phase 3 study TAF112582 Part 2 to serve as the basis for an NDA for the treatment of *P. vivax* malaria (radical cure).
23 January 2012 Type C Meeting	Agreement on a switch from the TQ capsule formulation to a tablet formulation without a Phase 3 bioavailability study on the condition that data from a Phase 1 study and/or a Phase 3 study (e.g. using sparse PK sampling) with the to be marketed tablet are available in the NDA.
15 January 2013	Orphan Drug designation for the treatment of malaria
13 November 2013 Type B Meeting End	Agreement on • the design of TAF112582 Part 2, a placebo controlled study of a single dose of

[12] Douglas NM, Poespoprodjo JR, Patrianai D, et al. Unsupervised PQ for the treatment of Plasmodium vivax malaria relapses in southern Papua: A hospital-based cohort study. PLOs Medicine 2017;14(8): e1002379
[13] Pereira EA, Ishikawa EA, Fontes CJ. Adherence to *Plasmodium vivax* malaria treatment in the Brazilian Amazon Region. Malar J. 2011;10:355.
[14] Maneeboonyang W, Lawpoolsri S, Puangsa-Art S, et al. Directly observed therapy with PQ to reduce the recurrence rate of Plasmodium vivax infection along the Thai-Myanmar border. Southeast Asian J Trop Med Public Health. 2011;42:9–18
[15] Takeuchi R, Lawpoolsri S, Imwong M, et al. Directly-observed therapy (DOT) for the radical 14-day PQ treatment of Plasmodium vivax malaria on the Thai-Myanmar border. Malar J. 2010;9:308.
[16] Khantikul N, Butraporn P, Kim HS, et al. Adherence to antimalarial drug therapy among vivax malaria patients in northern Thailand. J Health Popul Nutr. 2009;27:4–13.
[17] Abreha T et al. Comparison of artemether-lumefantrine and chloroquine with and without PQ for the treatment of Plasmodium vivax infection in Ethiopia: A randomized controlled trial PLoS Med. 2017 May 16;14(5)
[18] Grietens KP, Soto V, Erhart A, et al. Adherence to 7-day PQ treatment for the radical cure of *P. vivax* in the Peruvian Amazon. Am J Trop Med Hyg. 2010;82:1017–23.

Date	Key Discussion Points
of Phase II	300mg of TQ added to CQ. • inclusion of Phase 3 safety study (TAF116564) assessing the incidence of hemolysis with TQ compared to 14 days of PQ as a part of the NDA • a target Phase 3 safety database of 500 subjects exposed to 300mg TQ. • request for data on 300 subjects with adequate ophthalmic assessment
18 December 2013	Breakthrough Therapy designation
27 January 2015 Type C Meeting	Final agreement on design and timing of an ophthalmic safety study (Study 201807).
27 August 2015 Type C Meeting	Agreement on increasing recruitment of subjects in South America in Study TAF112582 Part 2 to 80%.
8 April 2016 Type C Written responses	Agreement on the following changes to the Phase 3 clinical program: • amended size of the clinical program to support a marketing application for TQ for the treatment of P. vivax malaria (485 subjects exposed to a single 300mg dose of TQ from studies TAF112582 Part 1 and Part 2 and TAF116564). • Study TAF116564 is to be submitted without data on 50 subjects with moderate G6PD deficiency due to recruitment difficulties. • a pretreatment diagnostic test for G6PD deficiency and instructions for prescribers in the PI would be important components of a risk management plan
23 February 2017 Type C Meeting	Agreement on study data integration, CRT packages and SAE/AE CRF reporting for both Phase 3 and supportive clinical data in other indications to be included in the planned NDA for TQ for the treatment of *P. vivax* malaria.
18 July 2017 Type B Meeting Pre-NDA	Agreement on the content of the planned NDA submission for TQ for the treatment (radical cure) of *P. vivax* malaria. (NDA 210,975)
19 January 2018	Priority Review Designation
12 July 2018	Antimicrobial Drug Advisory Committee meeting

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

4.1. Office of Scientific Investigations (OSI)

Study TAF112582 was audited at good clinical practice (GCP) inspections of two foreign clinical investigator (CI) sites selected based on: (1) lack of domestic CI sites, (2) high subject enrollment, and (3) foreign inspection feasibility. No significant deficiencies were observed at Site 87400 (CI Lacerda, Brazil) and a Form FDA 483 was not issued. At Site 87111 (CI Krudsood, Thailand), a Form FDA 483 was issued for minor GCP deficiencies unlikely to be significant to the study outcome. At both CI sites, study conduct appeared GCP-compliant, including sponsor oversight of study conduct. All audited data were acceptably verifiable against source records and CRFs. The data for Study TAF112582 appear reliable as reported in the NDA.

4.2. Product Quality

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

TQ tablet contains tafenoquine succinate, an antimalarial agent for oral administration. The chemical name of tafenoquine succinate is (±) 8-[(4-amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline succinate. The molecular formula for tafenoquine succinate is $C_{24}H_{28}F_3N_3O_3 \bullet C_4H_6O_4$, and its molecular mass is 581.6 as the succinate salt (463.5 as free base). The structural formula is shown below in Figure 1.

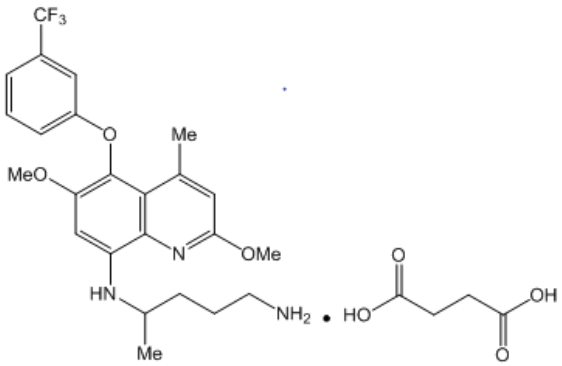


Figure 1 Structure of Tafenoquine succinate

For details of product quality assessment refer to the multidisciplinary quality assessment review by the Office of Product Quality (OPQ). A summary of the review findings is presented below.

The tafenoquine drug substance, (b) (4) is a pale green or pale orange to orange solid, very slightly soluble in water and soluble in methanol.

The drug product, an immediate release tablet for oral administration, contains 188.2 mg of tafenoquine succinate, equivalent to 150 mg tafenoquine free base. TQ tablet is a pink film coated, capsule shaped tablet, 17.1 mm by 9.0 mm, plain on one side and debossed with 'GS J11' on the other side.

Table 2 Quantitative Composition of KRITAFEL (tafenoquine succinate) Drug Product

Component	Quantity (mg/tablet)	Function	Reference to Standard
Tablet Core			
Tafenoquine Succinate[1]	188.2	Active	GSK
Microcrystalline Cellulose	(b) (4)		USP/NF
Mannitol			USP/NF
Magnesium Stearate			USP/NF
Total Core Weight			-

Component	Quantity (mg/tablet)	Function	Reference to Standard
Film Coating			
(b) (4)			Supplier
			USP/NF
Total Coated Tablet Weight	927.0	-	-

1 Equivalent to 150 mg tafenoquine (free base). The amount of tafenoquine succinate is calculated based on the molecular weight of tafenoquine succinate (581.6) and tafenoquine (463.5) with a salt to base factor of 0.797.
2 Film coat target is (b) (4)% weight gain based on tablet core weight (range: (b) (4)% w/w).
3 The components of (b) (4) are hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol and red iron oxide.
4 (b) (4) is removed during processing.
Source: Applicant's submission

The proposed commercial container closure for the drug product is (b) (4) high density polyethylene (HDPE) bottle with (b) (4) child-resistant c (b) (4) , and a (b) (4) . TQ tablets will be available in two packaging configurations: a patient pack containing two tablets and a pharmacy dispensing pack containing 30 tablets, each supplied in an HDPE bottle.

The drug substance and drug product proposed specifications, including the analytical procedures and validation data, were found acceptable by the review team.

Available stability data in the NDA support the proposed retest period of (b) (4) months for tafenoquine drug substance stored up to (b) (4) and p (b) (4) The stability of the proposed drug product, TQ tablets, 150 mg, packaged in the proposed container closure system in two configurations has also been demonstrated. The drug product release and stability data did not reveal any polymorphic changes. The proposed expiry dating of 24 months for the drug product packaged in HDPE bottles, and to be stored at controlled room temperature, has been found acceptable. The adequate in-use stability data support the proposed labeling for the pharmacy dispensing pack, including a statement that the product should be used within 3 months once the bottle is opened.

The commercial tafenoquine succinate drug substance manufacture (b) (4) and the drug product manufacturer is GlaxoSmithKline LLC, Zebulon, NC. The drug product GSK site, the drug substance P (b) (4) site, and testing facilities have been found acceptable.

(b) (4) as found acceptable by the OPQ process reviewer .

The biopharmaceutics review found the proposed dissolution method acceptable including agreed upon the acceptance criterion of Q= (b) (4)% at (b) (4) minutes. Based on the comparative in

vitro dissolution data, the bridging between the debossed film-coated tablets produced by the proposed commercial manufacturing site (GSK, Zebulon, NC) and the unmarked film-coated tablets produced by the Phase 3 clinical supply manufacturing site ((b) (4) was also found acceptable.

The Applicant's claim of categorical exclusion from the Environmental Assessment per 21 CFR 25.31(b) has been found acceptable.

The OPQ review team concluded that NDA contains sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, tafenoquine succinate tablets. The manufacturing and testing facilities for this NDA are deemed acceptable. From a Product Quality perspective, the NDA is recommended for approval.

4.3. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

TQ is an 8-aminoquinoline of the established pharmacologic class 'antimalarial'. The nonclinical safety profile consists of Pharmacology, Pharmacokinetics and Toxicology studies, *in vitro* and *in vivo*, in guinea pig, monkey, rabbit, dog, mouse and rat. Pivotal studies discussed in this NDA review include *in vitro* studies in human embryonic kidney-293 cells transfected with hERG cDNA, dog Purkinje fibers assays, single and repeat dose studies (up to 104 weeks); phototoxicity studies in mouse fibroblasts; fertility and pre- and post-natal developmental studies in rat; embryo-fetal developmental studies in rat and rabbit; genetic toxicology studies and carcinogenicity studies in rat and mouse.

Pharmacokinetics:

The rate of absorption of oral TQ was slow in all species with T_{max} generally ranging from 6 to 168 hours after dosing. Absorption was low, ranging from 15% (rat) to 40% (dog), based on total radioactivity in urine and bile after single doses of ^{14}C tafenoquine. C_{max} and AUC were generally proportional or supraproportional to dose. TQ is very highly protein bound (99.5%) and tissue distribution was widespread with highest concentrations observed in the lung, intestines, spleen, liver, kidneys and heart in descending order. Although only seen in low levels, drug related radioactivity in the brain indicated minimal penetration of the blood brain barrier. There was significant plasma accumulation (up to 10-fold) with repeat dosing. Although the applicant concluded that drug levels had achieved steady state after 8 weeks of repeat dosing, there was a 3-fold increase in AUC between Week 8 and Week 52 in the rat carcinogenicity study. In one study, the elimination $T_{½}$ (h) was calculated to be 193 hours in

monkeys and 315 hours in dogs. After oral administration, most of the absorbed TQ was excreted via the feces, principally as unchanged TQ. There are however a few metabolites formed via O-demethylation, O-dearylation, oxidation, oxidative deamination and/or glucuronidation. TQ levels were not evaluated in pregnant or nursing animals.

Safety Pharmacology:

TQ was a moderate inhibitor of the tail current in human embryonic kidney 293 cells (transfected with hERG cDNA) with an IC_{50} of 0.5 µg/mL (1.1 µM). TQ had no effect on action potential parameters in the dog isolated Purkinje fiber preparation at concentrations up to 10 µmol. There were no adverse effects on cardiovascular function in conscious beagle dogs receiving single oral doses of TQ up to 16 mg/kg, about 7 times the human dose based on C_{max} comparisons. Neurobehavioral assessments in rats conducted up to 48 hours after a single oral gavage dose of TQ (125, 250 or 500 mg/kg) showed lower numbers of mean horizontal movement count at doses 13 times the C_{max} at the recommended dose, but these effects were sporadic and variable. There were no other biologically significant effects. Behaviors observed included posture, eyelid closure, vocalization, motor movements, ease of removal, reactivity to handling, chromodacryorrhea, lacrimation, salivation, condition of coat, gait, posture, ease of locomotion, arousal, piloerection, exophthalmia, number of pools of urine, number of fecal pellets, unformed feces, fasciculation, tremors, convulsions, response to visual approach, auditory assessments, pinna reflex, proprioception, pain perception, pupil response, air righting, grip strength landing foot splay, body temperature and motor activity. A second study, which evaluated rats after multiple doses (juvenile into adulthood) found no effects on motor activity at doses with C max values at 7 times the recommended dose.

Repeat-Dose Toxicology Studies:

Erythrocytes, lungs, spleen, liver and kidneys were identified as the targets of TQ toxicity in repeat dose toxicity studies in rats, mice and dogs treated for up to 2 years. The findings are consistent with the cationic amphiphilic structure of TQ, with the associated phospholipidosis. In dogs, doses up to 4 mg/kg/day for 52 weeks resulted in blue tongue, increased methemoglobin, increased reticulocyte counts, reduced hematocrit, Heinz bodies, accumulation of foamy macrophages, interstitial inflammation in the lung and pigmentation (liver, kidney, spleen, gallbladder, tonsils and lymph nodes). Pigmentation, hemosiderin deposition, increased spleen weights and bone marrow hyperplasia were considered to be related to the toxic effects in the red blood cells, methemoglobinemia, Heinz bodies and reduced hematocrit. This toxicity to the red blood cells and phospholipidosis, (evidenced by foamy macrophages in the lung), may have contributed to the increased lung, liver and spleen weights observed. No NOAEL was determined because of Heinz bodies observed in low dose dogs. Tafenoquine toxicities were dose related and the high dose in the 13-week dog study (6mg/kg) was higher than the high dose in the 52-week study (4 mg/kg) and both doses resulted in excessive toxicities (reductions in body weight). No new toxicities were observed in the 52-week dog study compared to the 13-week study except for pigmentation in additional

tissues (kidney, gall bladder, lymph nodes) in the longer study. Similarly, in the rats, findings were also dose related and no new toxicities were observed in the 6-month study, compared to the 13-week study except that bone marrow hyperplasia was not seen in the 13-week study. A NOAEL could not be determined in the 6-month rat study based on the congestion, pigmentation and erythropoiesis in the spleen, and bone marrow hyperplasia in the low dose, (0.5 mg/kg/day) but the NOAEL was 0.5 mg/kg/day in the 13-week rat study, a dose estimated to be equivalent to the clinical exposure based on AUC data from the rat carcinogenicity study. The lack of a NOAEL in the 6-month study was not a concern since this product is indicated for single dose use and other studies have shown that these findings are either inconsequential (pigmentation) or reversible (all the other findings).
The main difference between the rats and the dogs was the presence of blue gum, tongue, and sclera in the dogs. In 13-week reversibility studies in rats and dogs, the findings observed at the end of 13 weeks were largely reversible after a 13-week recovery period, except for the hemosiderin deposits and changes in the macrophages.

Genetic Toxicology and Carcinogenicity:

Tafenoquine induced an equivocal increase in mutation frequency in L5178Y mouse lymphoma cells but was negative in the Ames assay, the *in vitro* chromosomal aberration assay in Chinese hamster ovary cells and the *in vivo* rat micronucleus assay. Tafenoquine administration was associated with an increase in renal cell adenoma/carcinoma (combined) in male rats in a 2-year carcinogenicity study, but the 2-year carcinogenicity study in mice was negative. The positive finding study in this two-year carcinogenicity study is not of concern since this is a single dose administration and malaria can be a life-threatening illness.

Reproductive Toxicology:

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

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

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

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

RECOMMENDATION
The applicant has provided sufficient nonclinical safety information on TQ to support approval for marketing in the U.S.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

Details of the primary pharmacology studies, such as mechanism of action studies, conducted with TQ can be found in Nonclinical Microbiology Section 8.1.

Secondary Pharmacology
No secondary pharmacology studies of TQ were conducted.

Safety Pharmacology

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

This study examined the effect of TQ at concentrations of 0.06, 0.19, 0.60 and 1.9 µg/mL on the human ether-a-go-go related gene (hERG) tail current in human embryonic kidney-293 (HEK-293) cells transfected with hERG cDNA. Compounds that inhibit the hERG current may prolong the cardiac action potential and the QT interval in patients. TQ inhibited the hERG current by 18 % at 0.06 µg/mL, 36 % at 0.19 µg/mL, 60 % at 0.60 µg/mL and 97% at 1.9 µg/mL compared to 18 % in vehicle controls (treated with 0.3 % DMSO). After correction for the effect of the vehicle, the IC_{50} for the inhibitory effect of TQ on the hERG potassium current was estimated to be 0.5 µg/mL. This IC_{50} value is approximately 500 times above the free C_{max} of 0.001 µg/mL at the clinical exposure based on a mean C_{max} of 0.2 µg/mL and plasma protein binding of 99.5%. following a single 300 mg dose in humans. Under identical conditions, the positive control (100 nM E-4031) inhibited hERG potassium current by 93.1% (n = 3), confirming the sensitivity of the test system.

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

This study evaluated the effects of TQ on intracellularly recorded action potential parameters (action potential duration at 60% and 90% repolarization [APD_{60} and APD_{90}], maximum rate of rise of the upstroke (MRD), upstroke amplitude (UA) and resting membrane potential (RMP) in the dog isolated Purkinje fiber preparation electrically stimulated at 1 and 0.2 Hz. Fibers were exposed to TQ at 1, 10 and 100 µM. At 1 and 10 µM, TQ had no effect on UARMP, or APD_{60} and APD_{90} at stimulation frequencies of 1 and 0.2 Hz. At 100 µM, TQ exposure resulted in variable decreases in RMP, UA and MRD. The effects observed with 100 µM TQ were not associated with significant changes in APD_{60} and APD_{90}, but these measurements may be unreliable because of the morphological changes in the action potential resulting from the reductions in RMP, UA and MRD. Purkinje fibers exposed to the positive control substance (dl-sotalol hydrochloride, 30 µM) showed statistically significant increases in action potential durations (APD_{60}, and APD_{90} +39% at 1Hz and APD_{60}, +88% and APD_{90} +73% at 0.2Hz. TQ had no effect at concentrations up to 10 µM (about 4.5 µg/mL or about 4500-fold above the free Cmax of 0.001 µg/mL (based on C_{max} of 0.2 µg/mL and measured plasma protein binding of 99.5%) following a single 300 mg dose in humans

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

This study evaluated the effects of single oral doses of TQ on cardiovascular function in conscious beagle dogs (n=4 per sex). Dogs received either placebo (gelatin capsule containing 1% (w/v) aqueous methylcellulose + 0.2% (v/v) Tween 80) or 0.5 mg/kg TQ (females) or 16 mg/kg (males). Observations (recorded for six hours immediately after capsule administration and for another six hours, seven days after the treatment) included clinical signs, systolic, diastolic and mean blood pressures, heart rate, lead II electrocardiogram and plasma concentrations of TQ. TQ had no significant effect on clinical signs, blood pressures, heart rate, ECG amplitudes, or ECG intervals. C_{max} and systemic exposure (**$AUC_{(0\text{-}168h)}$**) at the high dose (16 mg/kg, males) were 1.4 µg/mL and 116 µg.h/mL respectively. This C_{max}, was equivalent to about 7 times the C_{max} observed at the recommended human dose (0.2 µg/mL).

Tafenoquine succinate: Neurobehavioral assessment when administered orally in rats (2017N328989)

This neurofunctional assessment study evaluated the effect of a single oral gavage dose of TQ (125, 250 or 500 mg/kg) in Sprague Dawley rats (6/sex/dose group) and consisted of a functional observation of battery (FOB) performed pretest and at 0.5, 3, 6, 24 and 48 hours postdose and a 60-minute locomotor activity assessment performed following the FOB pretest and at 6, 24 and 48 hours postdose. Clinical observations, viability and, body weights were also recorded. On Days 4 and 8, 3 animals/sex were sacrificed and their brains fixed and subjected to histopathology examination. The 500 mg/kg dose exceeded the maximum tolerated dose as indicated by mortality (one high dose male and one high dose female) and a 16 to 18 %

decrease in body weight compared to controls on day 8. Lower numbers of mean horizontal movement count (-76% to -95%) were observed at ≥ 250 mg/kg at 24 hours postdose but was observed in all doses 48 hours after dosing. There were no drug-related effects in the FOB assessment. Hematoxylin and eosin stained sections of the brain showed no evidence of neurodegeneration or other morphological abnormalities and axon morphology (visualized by Bielschowsky's silver stain) was comparable between control and TQ-treated animals. The C_{max} observed in rats at the 125 mg/kg dose was 2.6 µg/mL, or 13 times the human C_{max} following a single 300 mg dose of TQ (0.2 µg/mL). Based on these results, the NOAEL for neurological function in female rats is 125 mg/kg and in male rats it is ≤ 125 mg/kg, about 13 times the recommended human dose based on C_{max} comparisons.

Cardiovascular and pulmonary effects of WR-238,605 succinate (RSD-1018RZ/1)

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

SB-252263-AX: Oral juvenile toxicity study in CRL:CD(SD) rat (2015 N 233460)
To assess latent effects of dosing in juvenile rats, TQ was administered orally, every five days to juvenile Crl:CD (SD) rats (10/sex/group at 0 (vehicle),5, 15 or 25 mg/kg/occasion) on postnatal day (PND) 7, 12, 17 and 22 after which the dose levels were then increased to 0 (vehicle) 10, 20 or 50 mg/kg/occasion on PND 27, 32, 37, 42, 47, 52,57 and 62. After at least two weeks without treatment, animals were subjected to a neurobehavioral functional assessment. TQ was not associated with any biologically significant effects on locomotor activity, pre-pulse inhibition of auditory startle response, learning and memory ability (Morris water maze) or brain histopathology. The NOAEL was 25/50 mg/kg, associated with a C_{max} of 1.4 µg/mL, about 7 times the C_{max} following a single 300 mg dose in humans (0.2 µg/mL).

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

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

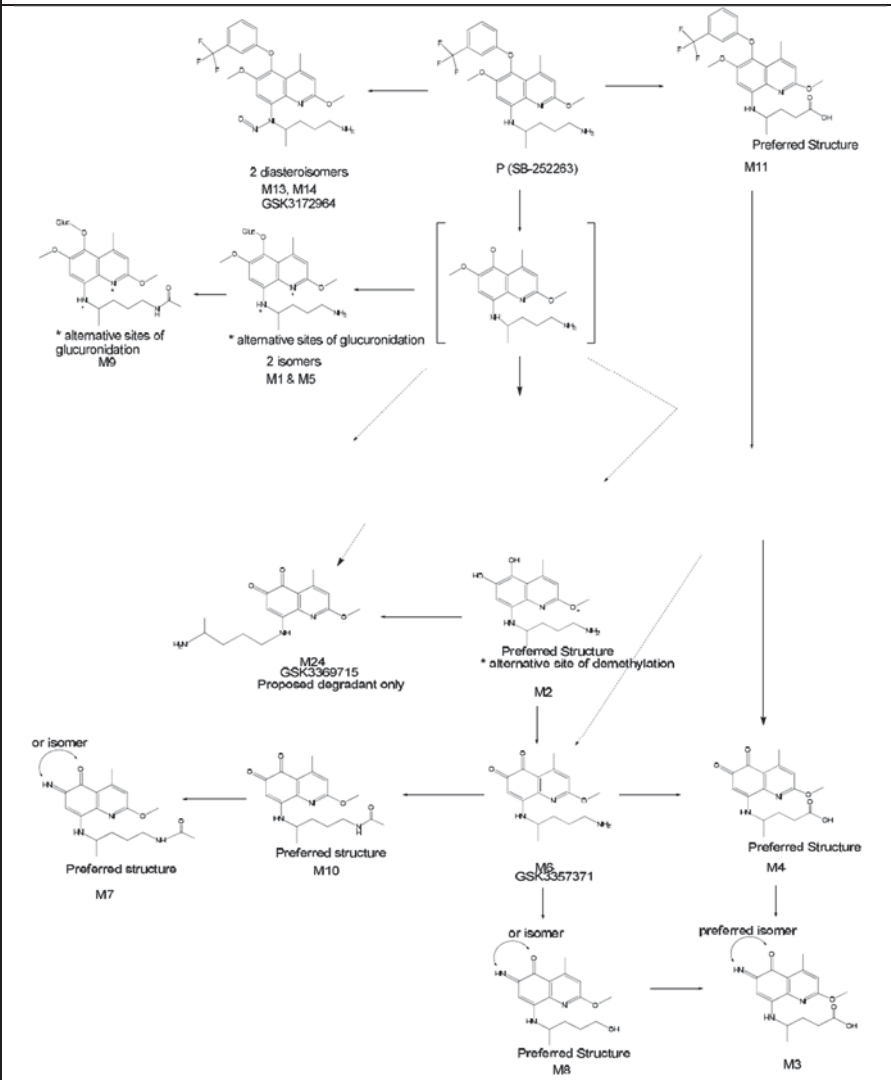
Test material	IC_{50} absence of UVA	IC_{50} presence of UVA	PIF value	MPE value
TQ	7	2	4	0.12
Chlorpromazine	22	1	22	N/A

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

5.4. ADME/PK

Table 3 Major Findings from ADME and PK in Nonclinical Studies

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

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>vitro plasma protein binding of [^{14}C]SB-252263 (TQ) in the rat, dog and man (RSD 1016rs)</td><td>
<table>
<tr><td>Human</td><td>99.5-100</td></tr>
<tr><td>Dog</td><td>99.7-100</td></tr>
</table>
</td></tr>
<tr><td>Metabolism</td><td></td></tr>
<tr><td>Preliminary quantification of the major metabolites of SB-252263 following oral administration of [^{14}C]SB-252263-AX to the male rat (2 mg free base/kg) and dog (1 mg free base/kg) RSD-101HHT/1</td><td> 
</td></tr>
<tr><td>Excretion</td><td></td></tr>
<tr><td>Elimination of Drug-Related Material Following a Single Oral Administration of [14C]SB-252263-AX to Male Rats at a Nominal Dose Level
of 2 mg free base/kg</td><td>Excretion in intact male rats Following a Single Dose of TQ
<table>
<tr><td>Excretion route</td><td>Recovery of Radioactivity (% Administered Dose)</td></tr>
<tr><td>Urine</td><td>7</td></tr>
<tr><td>Feces</td><td>67</td></tr>
<tr><td>GI tract</td><td>3</td></tr>
<tr><td>Carcass</td><td>13</td></tr>
<tr><td></td><td></td></tr>
</table>
Excretion in bile duct cannulated male rats Following a Single Dose
<table>
<tr><td>Excretion route</td><td>Recovery of Radioactivity (%</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>Administered Dose)</td></tr>
<tr><td>Urine</td><td>2</td></tr>
<tr><td>Feces</td><td>75</td></tr>
<tr><td>Bile</td><td>5</td></tr>
<tr><td>GI tract</td><td>1</td></tr>
<tr><td>Carcass</td><td>8</td></tr>
</table>
</td></tr>
<tr><td>The Metabolism and Pharmacokinetics of ^{14}C-WR 238605 in Beagle Dogs and in the Rhesus Monkey RSD 1016TH</td><td>
Pharmacokinetics in whole blood after Single Dose in beagle dog
<table>
<tr><td>Dose (mg/kg)</td><td>1.7</td><td>3.9</td><td>8.7</td><td>19.5</td></tr>
<tr><td>C_{max} [µg equivalent/mL]</td><td>0.5</td><td>0.9</td><td>5.6</td><td>5.5</td></tr>
<tr><td>AUC $_{(0-840)}$ (µg.h/mL)</td><td>168</td><td>386</td><td>2139</td><td>2416</td></tr>
<tr><td>T ½ (h)</td><td>275</td><td>315</td><td>175</td><td>230</td></tr>
</table>
Pharmacokinetics after a Single 1 mg/kg Dose in Monkey
<table>
<tr><td>Sample</td><td>Plasma</td><td>Blood</td></tr>
<tr><td>C_{max} [µg equivalent/mL]</td><td>0.15</td><td>0.15</td></tr>
<tr><td>AUC $_{(0-840)}$ (µg.h/mL)</td><td>32</td><td>36</td></tr>
<tr><td>T ½ (h)</td><td>165</td><td>193</td></tr>
</table>
</td></tr>
<tr><td>TK data from general toxicology studies
Rat: An 8-week oral gavage study in rats to investigate the pharmacokinetics of SB-252263 and the effect on hepatic levels of cytochrome P450 and related parameters.
• 0, 0.5, 2,9, mg/kg, daily
• Samples collected predose, 0.5, 1, 3, 5, 8, and 24 hrs. postdose
• RSD-1011XG/1</td><td>
Accumulation: Up to 10-fold over 56 days
Dose proportionality: C $_{max}$ and AUC $_{(0-24)}$ were approximately dose proportional

Toxicokinetic Parameters for 8-week oral gavage study in rats
<table>
<tr><td>Day</td><td>Dose</td><td>Sex</td><td>C_{max} [ng/mL]</td><td>T_{max} (h)</td><td>AUC $_{(0-24)}$ (µg.h/mL)</td></tr>
<tr><td>1</td><td>0.5</td><td>M
F</td><td>ND
ND</td><td>ND
ND</td><td>ND
ND</td></tr>
<tr><td></td><td>2</td><td>M
F</td><td>30
29</td><td>8
24</td><td>0.5
0.5</td></tr>
<tr><td></td><td>9</td><td>M
F</td><td>149
134</td><td>8
24</td><td>2.9
2.5</td></tr>
<tr><td>56</td><td>0.5</td><td>M
F</td><td>41
49</td><td>24
1</td><td>1
1</td></tr>
<tr><td></td><td>2</td><td>M
F</td><td>188
198</td><td>5
24</td><td>3.9
4.0</td></tr>
<tr><td></td><td>9</td><td>M
F</td><td>1176
1199</td><td>5
5</td><td>25
26</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>Rat: Oral juvenile toxicity study in CRL:CD(SD) rat
• 5, 15 or 25 mg/kg, (PND7 to 26) or 10, 20 or 50 mg/kg PND 27 to 62
• Plasma Samples collected 3, 8, 24, 72 or 120 hours after dosing.
• 2015N233460</td><td>
C_{max} at the highest dose was 1.4 µg/mL, about 7 times higher than the clinical dose, based on C $_{max}$ of 0.2 µg/mL following a single 300 mg dose in humans,

AUC $_{(0-168h)}$, T $_{max}$ and C_{max} data in juvenile rats
<table>
<tr><td>Dose (mg/kg)</td><td></td><td>5/10</td><td>15/20</td><td>25/50</td></tr>
<tr><td>AUC $_{(0-168h)}$ (µg.h/mL)</td><td>PND 7
PND 27
PND 62</td><td>19
11
19</td><td>58
27
37</td><td>89
66
100</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>
<table>
<tr><td>C_{max} (µg /mL)</td><td>PND 7
PND 27
PND 62</td><td>0.2
0.2
0.4</td><td>0.6
0.5
0.6</td><td>1.2
1.3
1.4</td></tr>
<tr><td>T_{max} (h)</td><td>PND 7
PND 27
PND 62</td><td>48
8
3</td><td>48
8
3</td><td>8
6
8</td></tr>
</table>
</td></tr>
<tr><td>Mouse: Two-month oral dose toxicokinetic study in mice

• 0.1, 0.3 or 1.0 mg/kg,
Samples collected Predose, 1, 2, 4, 6, 8, 12 and 24 hours after dosing on Week 8. RSD-101DSB/1</td><td>
Toxicokinetic Parameters for TQ in mice
<table>
<tr><td>Dose (mg/kg)</td><td></td><td>0.1</td><td>0.3</td><td>1.0</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>AUC $_{(0\text{-}8weeks)}$ (µg.h/mL)</td><td>M
F</td><td>14.5
8.5</td><td>42
25</td><td>137
91</td></tr>
<tr><td>AUC $_{(0\text{-}24h)}$ (µg.h/mL)</td><td>M
F</td><td>0.26
0.15</td><td>0.75
0.45</td><td>2.4
1.6</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>M
F</td><td>0.01
0.01</td><td>0.04
0.02</td><td>0.12
0.07</td></tr>
<tr><td>Tmax</td><td>M
F</td><td>8
12</td><td>12
12</td><td>12
6</td></tr>
</table>

NAUC (normalized AUC). The systemic exposure from the mouse, study is reported as AUC $_{(0\text{-}24\ h)}$ at day 56 following repeat dosing (considered to be at the point of steady state). The highest dose tested was about 1.2 times the clinical dose based on AUC $_{(0\text{-}24\ h)}$ comparisons.
</td></tr>
<tr><td></td><td></td></tr>
<tr><td>TK data from Carcinogenicity studies

Rat: 2 Year Oral oncogenicity Study with WR238605 succinate in Charles River CD rats
• 0, 0.1, 0.5, 1.0 and 2.0 mg/kg, daily
• Samples collected 1, 2, 4, 8, 12 and 24 hours after dosing on Week 8 and at Week 52
• RD2007/01198</td><td>
Accumulation: Up to 3-fold between Week 8 and Week 52 weeks.
Dose proportionality: C_{max} and AUC $_{(0\text{-}24)}$ were proportional or supraproportional to dose. The NOAEL was 0.5 mg/kg, which had an AUC $_{(0\text{-}24h)}$ of 1.8 µg*h/mL, which was similar to the clinical AUC $_{(0\text{-}24h)}$ of 1.7 µg*h/mL.

Pharmacokinetics parameters at 8 and 52 weeks in rat.
<table>
<tr><th>Week</th><th>Dose (mg/kg)</th><th>Sex</th><th>AUC $_{(0\text{-}24h)}$ (µg*h/mL)</th></tr>
<tr><td>8</td><td>0.1</td><td>M
F</td><td>0.05
0.05</td></tr>
<tr><td></td><td>0.5</td><td>M
F</td><td>1.0
1.5</td></tr>
<tr><td></td><td>1.0</td><td>M
F</td><td>2.8
3.6</td></tr>
<tr><td></td><td>2.0</td><td>M
F</td><td>6.3
7.3</td></tr>
<tr><td>52</td><td>0.1</td><td>M
F</td><td>0.2
0.2</td></tr>
<tr><td></td><td>0.5</td><td>M
F</td><td>1.8
1.8</td></tr>
<tr><td></td><td>1.0</td><td>M
F</td><td>4.2
5.5</td></tr>
<tr><td></td><td>2.0</td><td>M
F</td><td>8.7
12.7</td></tr>
</table>
</td></tr>
</table>

The systemic exposure from the mouse, rat and dog studies were reported as AUC $_{(0\text{-}24\ h)}$ at day 56 following repeat dosing (considered by the Applicant to be at the point of steady state). To evaluate the ratio of animal to human exposure, the AUC $_{(0\text{-}24\ h)}$ at day 56 have been scaled up (based on accumulative exposure, i.e. 56 x AUC $_{(0\text{-}24\ h)}$ to provide AUC 0-8 weeks at steady state and compared with AUC $_{(0\text{-}\infty)}$ in human following a 300 mg single dose. In one Phase I study[19], a single 300 mg dose of TQ, resulted in a mean C $_{max}$ of 0.2 µg/mL, a T $_{max}$ of 12 hours, an AUC $_{(0\text{-}\infty)}$: of 97 µg*h/mL and a t $_{½}$ of 375 hours. Alternatively, AUC $_{(0\text{-}24\ h)}$ was estimated to be 1.7 µg*h/mL (assuming AUC $_{(0\text{-}\infty)}$: of 97 µg*h/mL over 56 days).

5.5. Toxicology

5.5.1. General Toxicology

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

Key Study Findings

- The mid- and high doses exceeded the maximum tolerated dose as indicated by bodyweights which were more than 10 % lower than controls. Adverse effects at these doses included vomiting, diarrhea, reduced body weight, blue tongue, increased methemoglobin (3.5-13 % HGB), increased reticulocyte count, marginally reduced hematocrit (-13%) increased Heinz bodies (1.3 - 1.9% of RBCs), accumulation of foamy macro phages, interstitial inflammation in the lung, and pigmentation (liver, kidney, spleen, gallbladder, tonsil, and lymph nodes). The accumulation of foamy macro phages in the lungs reflect phospholipidosis, which is a well-known feature of cationic amphiphilic drugs such as TQ. Since Heinz bodies were present at the low dose, no NOAEL could be determined.
- Compared to the 13-week study, the only new findings were pigmentation of the kidneys and macrophages in the gall bladder and lymph nodes.
- Based on pharmacokinetics data from the 8-week dog study, (AUC $_{(0\text{-}24h)}$ of 0.9 µg*h/mL at 0.1 mg/kg), this LOAEL dose was about 0.5 times the clinical dose (AUC $_{(0\text{-}24h)}$ of 1.7 µg*h/mL).

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

Methods

[19] Phase 1, Five-cohort, Randomized, Open-label, Parallel-group Study to Evaluate the PK of a Single Dose of Tafenoquine 300 mg when Co-administered with Artemisinin-based Combination Therapies (ACT), Artemether + Lumefantrine (AL) and Dihydroartemisinin + Piperaquine tetraphosphate (DHA+PQP).

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

Observations and Results: changes from control

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

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

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

Key Study Findings

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

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

Methods

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

Observations and Results: changes from control

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

Parameters	Major findings
	MD: +340 % methemoglobin
Clinical Chemistry	HD: -15 % serum globulin, +62 % total bile acids, -23 % BUN
Gross Pathology	Unremarkable
Organ Weights	HD: +13 % kidney, + 97% Lung. +198 % spleen. + 34 % adrenal MD: +76 % Lung, +22 % spleen, +15 % adrenal
Histopathology **Adequate battery:** Yes	HD: Lung: foamy macrophage accumulation, chronic interstitial inflammation, and hemorrhage, Liver: apoptosis, pigmentation and fatty change, Spleen: congestion, hyperplasia, erythropoiesis, Kidney: pigmentation, Bone marrow: hyperplasia, granulopoiesis, adrenal gland pigmentation and congestion MD: Lung: foamy macrophage accumulation, chronic interstitial inflammation, Spleen: congestion, pigmentation, erythropoiesis, Kidney: pigmentation, Bone marrow: hyperplasia, Adrenal gland pigmentation and congestion. LD: Spleen: congestion, pigmentation, erythropoiesis, Bone marrow: hyperplasia .

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

General toxicology; additional studies

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

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

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

- Oral gavage administration of TQ at 0.1, 2, and 6 mg/kg/day for 13 weeks resulted in dose related adverse events, mostly in the mid and high dose including decreased body weight , methemoglobinemia (with blue gums, blue tongue, blue sclera,), hemolytic anemia (evidenced by reticulocytosis, bone marrow hypercellularity, decrease in bone marrow myeloid/erythroid (M/E) ratio, splenomegaly, extramedullary hematopoiesis, and hemosiderosis in the liver and spleen), leukocytosis, alveolar proteinosis (phospholipidosis), inflammation of the lung, increased kidney weight, hepatotoxicity (liver hypertrophy, subacute inflammation, hemosiderin deposit). . These findings were not detected in dogs after a 13-week recovery period, except for minimal/mild inflammation in the lungs and hemosiderin deposit in the liver of a few mid- and high-dose animals. No NOAEL was determined since Hemosiderin deposit and minimal liver inflammation were seen in single low dose animals. Based on pharmacokinetics data from the 8-week dog study, ($AUC_{(0\text{-}24h)}$ of 0.9 µg*h/mL at 0.1 mg/kg), this LOAEL dose was about 0.5 times the clinical dose ($AUC_{(0\text{-}24h)}$ of 1.7 µg*h/mL).

5.5.2.Genetic Toxicology

In Vitro

SB-252263 -AX (hydrogen succinate salt, PQ analog) (TQ): Microbial Mutagenicity study (Study # V23828)

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

Study title: Chromosomal Aberrations in Chinese hamster ovary cells (CHO) cells. (Study # G94BE97.330)
Key Study Findings: Negative
GLP compliance: Yes.
Test system: Chinese Hamster Ovary (CHO-K1) cells; up to 11 µg/mL; +/-S9
Study is valid: Yes

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

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

-

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

The result was equivocal since the mean mutant frequency was ≥ two-fold of the mean vehicle control mutant frequency (37 $x10^{-6)}$ at only one concentration (2.5 µg/mL) with 10% or greater total growth (16%). The increase in mean mutant frequency of ≥ two-fold of the mean vehicle control mutant frequency occurring at 5 µg/mL was not considered biologically relevant since these conditions resulted in excessive toxicity as indicated by less than 10% total growth.

Table 4: **Mean total growth and mean mutant frequency in mouse lymphoma cells treated with TQ**

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

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

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

<u>In Vivo</u>

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

-

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

5.5.3.Carcinogenicity

Two-year mouse carcinogenicity study

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

Two-year rat carcinogenicity study

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

Table 5: Renal adenoma and carcinoma in two-year rat carcinogenicity study

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

GLP compliance: Yes.
Definitive Doses: Males and females: 0.1, 0.5, 1.0, 2.0 mg/kg/day.
FDA Dose Concurrence: Yes, Based on data from study #152 (6-month rat study). NOAEL was 0.5 mg/kg ($AUC_{0\text{-}24h}$ of 1.8 µg.h/mL which was similar to the clinical exposure ($AUC_{0\text{-}24h}$ of 1.7 µg.h/mL at the recommended clinical dose

5.5.4.Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

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

Key Study Findings

- TQ treatment had no effect on mating or pregnancy at any dose despite maternal toxicity at the high dose (mortality, reduced weight gain, minimally reduced numbers of

corpora lutea, minimally reduced numbers of implantation sites and minimally reduced number of viable fetuses at the 15 mg/kg dose).

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

Methods

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

Embryo-Fetal Development

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

Key Study Findings

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

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

Methods

Dose and frequency of dosing:	0, 3, 10, and 30 mg/kg; daily. Positive controls: 1000 mg/kg/day Vitamin A
Route of administration:	Oral gavage
Formulation/Vehicle:	Aqueous 1% methylcellulose/0.2% (w/w) Tween® 80
Species/Strain:	CD rat from (b) (4)
Number/Sex/Group:	25
Study design:	Daily doses were administered by oral gavage from GD 6 to 15. Animals examined on GD 20 after cesarean section
Deviation from study protocol affecting interpretation of results:	No

Table 6: Effect of TQ on reproductive parameters in pregnant rats

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

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

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

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

- In high-dose dams, adverse effects included mortality abortion, decreased body weight and decreased food consumption.
- One mid-dose and 3 high-dose dams aborted and were sacrificed early. While the high dose animals experienced severe maternal toxicity (including mortality and reduced the body weight gain), TQ could not be ruled out as the cause of the mid-dose abortion.

- The NOAEL for maternal toxicity was 7 mg/kg (about 0.4 times the recommended human dose based on body surface area comparisons) and for embryofetal toxicity was 2 mg/kg (0.1 times the human dose).
- Since these findings were observed in animals that received at least 12 doses, it is not clear if these findings are likely to be observed in patients receiving the recommended single dose.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

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

Observations and Results

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

Table 7: Clinical signs in pregnant TQ treated rabbits

	0	2	7	25/16*	Vitamin A
Females pregnant/on study	18/20	15/20	16/20	19/20	18/20
Scheduled sacrifice	18	15	15	12	18
Animal found dead	0	0	0	2	0
Sacrifice moribund	0	0	0	2	0
Sacrificed/abortion	0	0	1	3	0
Premature delivery	0	0	0	1	0
Total body weight gain (kg)	0.36	0.34	0.33	0.18	0.30
Food consumption (Day 18)	130	130	130	68	

*Retest animals.

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

Table 8: Pregnancy outcomes in TQ treated rabbits

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

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

Table 9: Summary of cesarean section data from rabbits treated with TQ during organogenesis

Dose (mg/kg)	0	2	7	25*	25/16	Vit. A
Females pregnant/on study (n)	18/20	15/20	16/20	16/20	19/20	18/20
Died or euthanized moribund	0	0	0	2	4	0
Abortions/ litters evaluated	0/18	0/15	1/16	3/16	3/19	0/18

Dose (mg/kg)	0	2	7	25*	25/16	Vit. A
Viable fetuses (n)	7.8	8.1	7.4	7.8	9.5	5.7
Post implantation loss (%)	6	2	6	8	4	23
External malformations (% litters)	0	0	0	0		77
Skeletal malformations (% litters)	11	27	33	Not performed	17	88
Visceral malformations (% litters)	0	7	0	0	0	53

Prenatal and Postnatal Development

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

Key Study Findings

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

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 2, 6, and 18 mg/kg; daily
Route of administration: Oral gavage
Formulation/Vehicle: 1% Methylcellulose/0.2% Tween® 80
Species/Strain: Rat, CD © (from (b) (4)
Number/Sex/Group: 25
Study design: Pregnant females (F_0) were dosed daily from GD 0 through PND 20

F_o data included mortalities, clinical observations, body weight, food consumption, reproductive parameter and gross necropsy observations. Dams euthanized on PND21.
F1 data included mortalities, clinical observations, body weight, preweaning survival, developmental parameters, functional

	observation battery, motor activity, learning, memory, reproductive parameters and gross necropsy observations. F_1 offspring (F_2) were sacrificed after examination on the day of parturition
Deviation from study protocol affecting interpretation of results:	None

Observations and Results

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

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

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

Table 10: Body weights and rearing posture in pups born to TQ treated rats

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

F2 Generation	Unremarkable

5.5.5.Other Toxicology Studies

Local Tolerance

TQ was classified as a mild irritant following a four-hour exposure of an aqueous solution to intact rabbit skin. It is classified as a moderate irritant to abraded skin (Acute skin irritation study in the rabbit. Study 061/1386). In the 'Acute eye irritation test in the rabbit' (Study 061/1387), TQ was classified as a severe irritant.

Impurity Qualification

There are no mutagenic impurities in the proposed tafenoquine Drug Substance Specification. The 4 specified non-mutagenic impurities (b) (4)

(b) (4) in the proposed tafenoquine drug substance specification will be maintained at levels below the ICH Q3A(R2) quantification limit ((b) (4) w/w). All other unspecified impurities will be maintained at levels (b) (4) w/w in accordance with ICH Q3A.

6 Clinical Pharmacology

6.1.1. Executive Summary

The Office of Clinical Pharmacology (Division of Clinical Pharmacology IV, Division of Pharmacometrics, and Genomics and Targeted Therapy Group) reviewed the information contained in NDA 210795. The clinical pharmacology information submitted in the application supports the approval of KRINTAFEL (tafenoquine, TQ) tablets as a single-dose regimen in combination with CQ for the radical cure of *P. vivax* malaria in patients aged 16 years and older.

Table 11: Summary of OCP's Recommendations & Comments on Key Review Issues

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The pivotal evidence of effectiveness of TQ in patients with *P. vivax* was supported by one Phase 3 trial (Study TAF112582, Part 2). Supportive evidence of effectiveness was provided by a Phase 2b dose ranging trial (Study TAF112582, Part 1), a Phase 3 safety trial (Study TAF116564), and the exposure-response analysis for efficacy.
General dosing instructions	The recommended dosing regimen is a single 300-mg dose (two 150-mg tablets) taken with food. KRINTAFEL should be co-administered with CQ on the first or second day of CQ administration.
Dosing in patient subgroups (intrinsic and extrinsic factors)	TQ is contraindicated in patients with G6PD deficiency.
Labeling	The Applicant's proposed labeling is generally acceptable. The Applicant defined G6PD deficiency as G6PD enzyme activity <70% of normal. The review team recommends removing the proposed 70% cut-off from the Warning and Precautions section of the proposed labeling. In addition, the review team has specific content and formatting change recommendations that were communicated to the applicant.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed tablet formulation was used in Phase 3 trials (Study TAF112582, Part 2, and Study TAF116564). The capsule formulation was used in the Phase 2b dosing ranging trial (Study TAF112582, Part 1). There is no clinically significant difference in TQ exposure between the capsule

	and to-be-marketed tablet formulations based on population PK analysis.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Table 12: Summary of the clinical pharmacokinetics of TQ

Absorption	Slowly absorbed following oral administration, median T_{max} of 15 hours post-dose at 300 mg. When TQ was administered at 200 mg as a capsule with a high fat meal, TQ plasma AUC and C_{max} increased on average by 41% and 31%, respectively, as compared to the fasted state. Similar food effect is expected for the to-be-marketed tablet formulation.
Distribution	Plasma protein binding >99.5% Apparent oral volume of distribution >1,500 L Whole blood concentrations were 67% higher than plasma concentrations
Elimination	Mean terminal half-life approximately 15 days Clearance is approximately 3 L/h
	Metabolism Slow and negligible metabolism in vitro in human liver microsomes and hepatocytes No major systemic metabolites observed in blood or plasma following oral administration
	Excretion The excretion pathway of TQ in humans is unknown.

Source: NDA 210795

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant's proposed dosage regimen of KRINTAFEL is a single 300-mg dose (two 150-mg tablets) taken with food. KRINTAFEL should be co-administered with CQ on the first or second day of CQ administration.

The Applicant's proposed dosing regimen is supported by the efficacy, safety, as well as exposure-efficacy analyses from the clinical trials submitted in the NDA.

Therapeutic Individualization

G6PD Deficiency
As TQ has the potential to cause drug-induced hemolysis in patients with a deficiency in G6PD enzyme activity, TQ is contraindicated in patients with G6PD deficiency.

Outstanding Issues

Effect of TQ on substrates of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), Organic anion transporting polypeptide 1B1/1B3 (OATP1B1/ OATP1B3) has not been assessed.

6.3.Comprehensive Clinical Pharmacology Review

6.3.1.General Pharmacology and Pharmacokinetic Characteristics

Table 13: General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	TQ is an 8-aminoquinoline antimalarial that eradicates *P. vivax* liver hypnozoites, preventing the relapse of malaria.
Active Moieties	Tafenoquine
QT Prolongation	At a cumulative dose of 1,200 mg (400 mg/day for 3 days; 4 times the recommended dose), TQ did not prolong the QT interval to any clinically relevant extent.
General Information	
Drug exposure following the therapeutic dosing regimen	Following oral administration of a single 300 mg TQ in healthy subjects (Study 200951), TQ plasma C_{max} and $AUC_{0\text{-}inf}$ were 200 (20.0) ng/mL and 97196 (24.1) h·ng/mL [Geometric mean (CV%)], respectively.
Healthy vs. Patients	TQ C_{max} is approximately 65% higher in malaria patients (330 ng/mL, based on population PK analysis using data from Study TAF112582 Part 2) compared to healthy subjects (Study 200951). The observed higher C_{max} in malaria patients may be, in part, due to co-administration of CQ. Results from the drug-drug interaction study showed a 38% increase in TQ C_{max} when TQ was coadministered with CQ (Study TAF106491). There is no difference in TQ AUC between healthy subjects and malaria patients.
Dose Proportionality	Following oral administration, TQ AUC increased proportionally to dose over the dose range of 100 mg to 400 mg (Study SB252263/052).
Variability	Healthy subjects following TQ 300 mg single dose (Study 200951 TQ alone arm, N=24): CV% 24.1% for Cmax, CV% 20.0% for $AUC_{0\text{-}inf.}$
T_{max}	Median T_{max} of 15 hr at 300 mg (Study TAF114582)

<table>
<tr><td rowspan="4">Food effect</td><td colspan="3">PK Parameter Following 200 mg Oral Capsule</td></tr>
<tr><td>AUC_{0-inf} (mean ± SD)</td><td>T_{max} (median, range)</td><td>C_{max} (mean ± SD)</td></tr>
<tr><td>Fasted: 51.1 (22)
Fed: 69.7 (24.2)</td><td>Fasted: 13 (6-72)
Fed: 14 (5.63-144)</td><td>Fasted: 122 (43)
Fed: 166 (84)</td></tr>
<tr><td colspan="3">Point estimates (90% confidence intervals)
1.41 (1.15-1.72) | 1.31 (1.07-1.62) | Not reported
AUC_{0-inf} and C_{max} values for TQ were on an average 41% and 31% higher under fed conditions (Study SB-252263/022). This study was conducted with a capsule formulation rather than the to-be-marketed tablet formulation. Similar food effect is expected for the to-be-marketed tablet formulation.</td></tr>
<tr><td>Volume of Distribution</td><td colspan="3">Apparent oral volume of distribution >1,500 L based on population PK analysis</td></tr>
<tr><td>Plasma Protein Binding</td><td colspan="3">>99.5%</td></tr>
<tr><td>Substrate transporter systems [in vitro]</td><td colspan="3">Unknown</td></tr>
<tr><td colspan="4">Elimination</td></tr>
<tr><td>Half-life</td><td colspan="3">Approximately 15 days</td></tr>
<tr><td colspan="4">Metabolism</td></tr>
<tr><td>Fraction metabolized (% dose)</td><td colspan="3">Unchanged TQ was the only notable drug-related component detected in human plasma (Study SB252263/014 and Study RSD-101GZN).</td></tr>
<tr><td>Primary metabolic pathway(s) [in vitro]</td><td colspan="3">TQ metabolism is slow and negligible in vitro.</td></tr>
<tr><td colspan="4">Excretion</td></tr>
<tr><td>Primary excretion pathways (% dose)</td><td colspan="3">The primary excretion pathways of TQ in humans are unknown.</td></tr>
<tr><td colspan="4">In vitro interaction liability (Drug as perpetrator)</td></tr>
<tr><td>Inhibition/Induction of metabolism</td><td colspan="3">TQ demonstrated in vitro inhibition of several cytochrome P450 isoenzymes (CYPs) including 1A2, 2D6, 2C8, 2C9 and 3A4 enzymes. Oral administration of TQ did not have a clinically significant effect on substrates of CYP1A2 (caffeine), CYP2D6 (desipramine), CYP2C8 (CQ), CYP2C9 (flurbiprofen), or CYP3A4 (midazolam, CQ).

Oral administration of TQ did not have clinically significant effects on the pharmacokinetics of artemisinin based combination therapies (ACTs) including dihydroartemisinin, piperaquine, artemether, and</td></tr>
</table>

	lumefantrine.
Inhibition/Induction of transporter systems	In vitro, TQ inhibited metformin transport via human organic cation transporter-2 (OCT2), multidrug and toxin extrusion-1 (MATE1) and MATE2-K transporters. Risk assessments based on plasma concentrations (unbound C_{max}) of TQ at 300 mg single dose, compared with the in vitro IC_{50} values indicated a low in vivo DDI potential with OCT2 and MATE substrates.

6.3.2.Clinical Pharmacology Questions

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

The primary evidence of effectiveness of TQ for the radical cure of *P. vivax* malaria was provided by one Phase 3 study (Study TAF112582, Part 2). Supportive evidence of effectiveness was provided by the following two studies in patients with *P. vivax* malaria: one Phase 2b dose ranging study TAF112582, Part 1, and one Phase 3 safety study TAF116564.

The exposure-response (E-R) analysis based on pharmacokinetic (PK) and efficacy data from the Phase 2b dose ranging study (TAF112582 Part 1) provided additional supportive evidence of effectiveness of TQ as 300 mg single dose in combination with CQ for radical cure of *P. vivax* malaria. (See Clinical Pharmacology Question 2 for details).

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

Yes, the proposed dosing regimen of TQ is acceptable for adults and adolescents (aged 16 years and older) with *P. vivax* malaria:

- A single 300-mg dose (two 150-mg tablets) of KRINTAFEL taken with food.
- Coadminister KRINTAFEL on the first or second day of CQ administration.

The primary efficacy endpoint used in Phase 2b and Phase 3 studies (TAF112582 Part 1 and Part 2) was recurrence-free efficacy at six months postdosing.

In the placebo-controlled phase 3 study, TAF112582 part 2, TQ at 300 mg single dose in combination with CQ demonstrated a clinically and statistically significant reduction in the risk of recurrence (75.9%, 95% CI: 61.8%, 84.8%; $p<0.001$) compared with CQ alone. The dose for Phase 3 was selected based on Phase 2b results.

Phase 2b dose ranging study, TAF112582, Part 1, evaluated the efficacy and safety of TQ at 50, 100, 300, and 600 mg single dose in combination with CQ. Results from this study show that both 300 and 600 mg doses were associated with high response rate (Table 14). In addition, the recurrence-free rate appeared to reach a plateau at 300 mg regardless of region. Little efficacy improvement was observed when TQ dose increased from 300 mg to 600 mg.

Table 14: Recurrence-Free Efficacy over 6 Months (Kaplan-Meier Methodology) by Country

Dose	Placebo	50 mg	100 mg	300 mg	600 mg
% Recurrence-free at 6 month	37.5% (N=54)	57.7% (N=55)	54.1% (N=57)	89.2% (N=57)	91.7% (N=56)
% Recurrence -free at 6 month, By Country					
Brazil	16.7% (N=6)	33.3% (N=6)	33.3% (N=6)	83.3% (N=6)	85.7% (N=7)
Peru	12.2% (N=22)	45.5% (N=22)	39.5% (N=24)	81.1% (N=23)	84.0% (N=23)
Thailand	56.3% (N=16)	60.0% (N=16)	67.3% (N=16)	94.7% (N=19)	100% (N=16)
India	90.0% (N=10)	90.9% (N=11)	80.0% (N=11)	100% (N=9)	100% (N=10)

Source: Applicant's report for Study TAF112582 Part 1

Exposure-Response Analysis for Efficacy

The review team conducted an independent exposure-response (E-R) analysis using data from Study TAF112582 Part 1 by excluding Indian patients due to high response rates in both placebo (CQ alone) and treatment (TQ plus CQ) arms in Indian sites.

Figure 2 shows the results of logistic regression analysis on the relationship between TQ AUC and recurrence-free rate at 6 months. As shown in Figure 2, TQ exposures at doses lower than 300 mg (50 and 100 mg) were associated with a relatively low response rate while the exposures with doses of 300 mg and 600 mg were associated with a high and flat response. These results confirmed that the recurrence-free rate at 6 months reached a plateau with a dose of 300 mg or higher. Similar results were observed when E-R analysis for recurrence-free rate at 6 months was further conducted by country (See Appendix 16.4 for details).

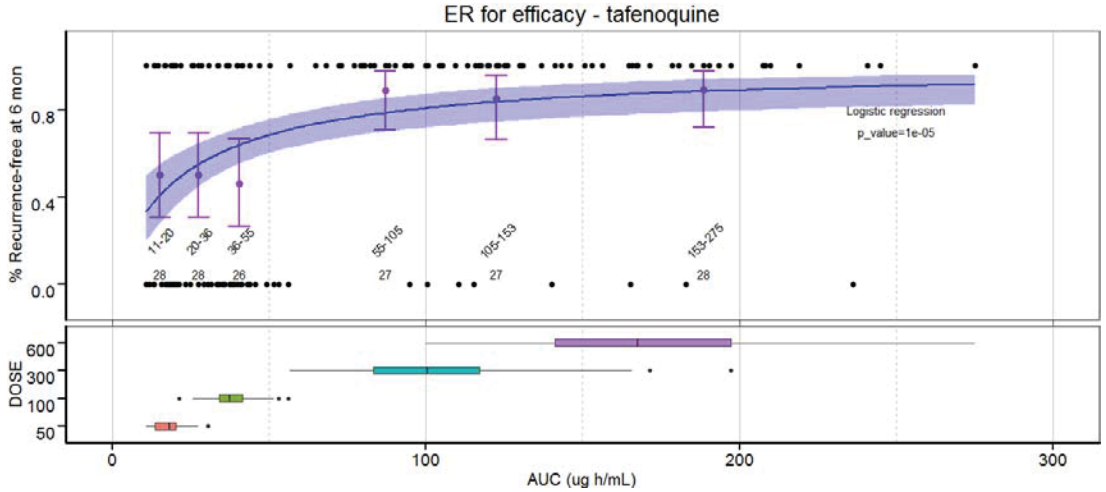


Figure 2: Exposure-Response Relationship for Recurrence-free Rate at 6 Months from Study TAF112582 Part 1

E-R analysis was also conducted using a time-to-event approach where time to recurrent malaria was coded as an event and subjects with no recurrent malaria were censored. Results of the time-to-event analysis suggest that the relatively high recurrence-free rate by 6 months is achieved at AUC bins of 66 µg·h/mL and above (Figure 3). In addition, the responses are similar between AUC bins 66-127 µg·h/mL and 127-275 µg·h/mL and appear to plateau at AUC greater than 66 µg·h/mL. The median (90% prediction interval) of AUC at TQ 300 mg single dose was estimated to be 104 (61.1-152) µg·h/mL in Study TAF112582 Part 2. This indicates that sufficient drug exposure can be achieved with a 300 mg single dose to provide maximum recurrence-free rate at 6 months in patients with *P. vivax* malaria. Thus, the results of time-to-event analysis are consistent with those from the logistic regression analysis, supporting the 300 mg TQ dose for the radical cure of *P. vivax* malaria.

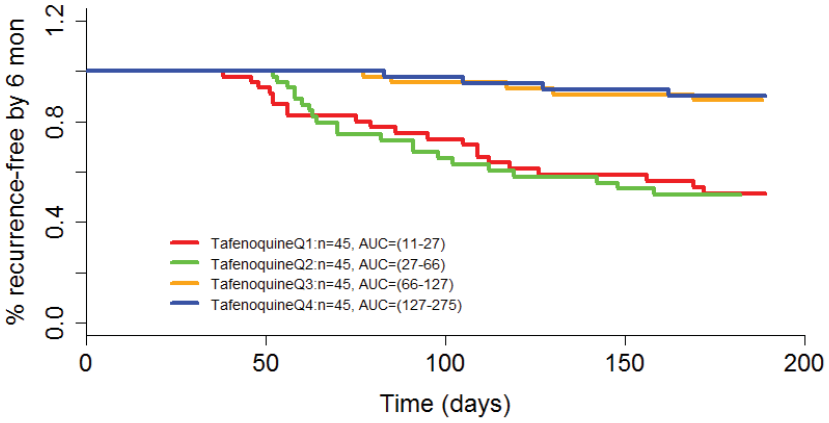


Figure 3: Time to Event Analysis for Recurrence-free Rate at 6 Month from Study TAF112582 Part 1

Different oral formulations were used in the Phase 2b dose ranging study (TAF112582 Part 1, capsule formulation) and Phase 3 studies (tablet as the to-be-marketed formulation). TQ exposures were determined to be comparable between these two formulations (116% (111-120%) [median (90% CI)], tablet vs. capsule) via population PK analyses (See Appendix 16.4). Therefore, similar results from the E-R analysis would be expected if the tablet formulation of TQ were used in the dose ranging study.

Safety

As an 8-aminoquinoline antimalarial, the primary safety liability for TQ is drug-induced hemolysis in patients with G6PD deficiency. Hence, patients with G6PD deficiency were excluded from Phase 2b and Phase 3 studies (Study TAF112582, Part 1 and Part 2). Study TAF116564 was conducted to compare the hemolytic effect of TQ (300 mg single dose) and PQ in subjects with and without G6PD enzyme deficiency. However, the study was not able to recruit sufficient number of subjects with G6PD deficiency (only 1 recruited). The overall incidence of clinically relevant hemolysis, defined as a decrease in hemoglobin of ≥30% or >3

g/dL from baseline or an overall drop in hemoglobin to below 6.0 g/dL, was 2.4% and 1.2% in TQ+CQ and PQ+CQ treatment groups, respectively. No subjects needed blood transfusion.

A Phase 1 study (Study TAF110027) was conducted to investigate the hemolytic potential of TQ given as 100, 200 and 300 mg single doses to female healthy volunteers with and without heterozygous G6PD deficiency (40–60% of site median). The study also evaluated PQ 15 mg once daily × 14 days as a positive control. Results from this study showed that there was a dose dependent decline in hemoglobin from baseline in G6PD deficient subjects as compared to those with normal G6PD activity. The highest median hemoglobin declines were observed in G6PD deficient females in both TQ 300 mg and PQ groups. Therefore, TQ must not be administered to subjects with G6PD deficiency.

In addition, small declines in hemoglobin were also observed in G6PD-normal subjects receiving TQ, with greater decrease in hemoglobin (1 vs. 0.4 g/dL) at 1200 mg (400 mg once daily for 3 days) versus 300 mg single dose (Study TAF114582). Although the extent of decline in hemoglobin observed in G6PD normal subjects is not considered clinically significant, these results suggest that doses higher than 300 mg may also have increased risk of hemolysis in subjects with normal G6PD activity.

Quantitative G6PD tests may not be available in all endemic countries. TQ, intended for single one-time dose, has a long half-life (about 15 days). Once administered, treatment cannot be withdrawn; persistent drug exposure is expected to be maintained for a long period of time, which could cause further decline in hemoglobin in patients with G6PD deficiency especially at doses higher than 300 mg. Hence, considering the potentially higher risk of hemolysis and the minimal improvement in efficacy with the 600 mg dose, a higher dose of TQ (e.g., 600 mg) appears to have limited benefit in patients with *P. vivax* malaria.

Conclusion

Taken together, the efficacy and safety results of TQ at 300 mg single dose, the exposure-response analysis for efficacy, and the potential risk of hemolysis with doses higher than 300 mg, the proposed 300 mg single dose of TQ in combination with CQ for the general patient population (i.e., non-G6PD deficient) is acceptable from a Clinical Pharmacology perspective.

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

G6PD Deficiency

TQ exposure was similar in subjects with and without G6PD deficiency (TAF110027). However, patients with G6PD deficiency must not take TQ due to its potential for drug-induced hemolysis (See Clinical Pharmacology Question 5 for details).

Hepatic and Renal Impairment

The review team concurs with the Applicant's proposal that no dose adjustment is needed in patients with hepatic and/or renal impairment, in part because TQ is administered as a single one-time dose. In addition, TQ undergoes minimal hepatic metabolism based on data from in vitro hepatocyte and microsomal studies and kidney is not identified as the major elimination organ based on the currently available data (Study RSD-101GZN). Furthermore, no significant QTc prolongation effect and other safety concerns of TQ were observed at supratherapeutic dose of 1200 mg (400 mg once daily for 3 days) (Study TAF114582 and Study SB252263/015). These results suggest that significant safety concerns are not expected at TQ 300 mg single dose in the event of prolonged drug elimination that may occur in patients with hepatic and/or renal impairment.

Other Intrinsic Factors (Age, Sex, Ethnicity and Body Weight)

Based on the population PK analysis, PK of TQ is not significantly impacted by age, sex, ethnicity, and body weight to the extent that dose adjustment is needed (See Appendix 15.4). The PK/Efficacy/Safety database was representative of the US population with respect to race, sex and weight. Majority of the subjects were non-elderly adults.

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

Food Effect

Food intake increases TQ exposures. TQ is recommended to be taken with food to increase systemic absorption and minimize gastrointestinal side effects.

The applicant conducted a food effect study with the 200 mg capsule formulation (Study SB-252263/022). Results from this study showed that total TQ exposure ($AUC_{0-\infty}$) was increased approximately 41% under fed (high-fat, high-calorie) conditions (Table 15). It should be noted that prior to the Phase 3 studies, the formulation was changed from capsules to tablets (to-be-marketed formulation; 150 mg immediate release tablet). The applicant did not conduct a separate food effect study with the to-be-marketed tablet formulation. This tablet formulation was administered only under fed condition in all clinical studies. The TQ exposures under fed condition across these two formulations were found to be comparable based on results from population PK analyses (See Appendix 16.4).

Table 15: Mean (SD) Pharmacokinetic Parameters Following 200 mg Single TQ Dose Administration (Capsule) to Healthy Male and Female Volunteers in the Fasted and Fed States

Parameter	Fasted (n=20)		Fed (n=20)	
	Value (mean, SD)	CV%	Value (mean, SD)	CV%
$AUC_{(0\text{-}inf)}$ µg.h/mL	51.1 (22)	49.8	69.7 (24.4)	31.3
Cmax, ng/mL	122 (43)	47.2	166 (84)	43
Tmax*, h	13 (6-72)	NA	14 (5.62-144)	NA
$t_{1/2}$, days	15.4 (2.6)	NA	15.5 (11.6)	NA

*Data presented as median (range)

NA: Not available
Source: Table 1 in the Study report of Study SB-252263/022

Food Effect for The To-Be-Marketed Tablet Formulation
Results from the food effect study using the capsule formulation were extrapolated to the to-be-marketed tablet formulation based on physicochemical properties of TQ, formulation comparisons, and efficacy results noted in the Phase 3 trials wherein tablets were administered with food.

TQ succinate is a weak base (pKa values reported as 3.0 and 10.0 on two separate measurements) and has higher solubility under acidic conditions (simulated gastric fluids at a pH of 1.6). It becomes only sparingly soluble at a pH of 2 and practically insoluble above a pH of 6 when dissolved in aqueous media. The Sponsor was unable to reliably determine permeability values for TQ due to drug trapping inside of cells and has therefore classified TQ succinate as a BCS Class 2 or a BCS Class 4 compound.

Like most drugs with a pH-dependent solubility profile, TQ is susceptible to precipitation with increased postprandial intestinal pH. The precipitated drug exists as aggregates of fine particles and may only partially re-dissolve in the GI tract due to limited solubility under the conditions associated with elevated pH. This leads to incomplete absorption under fasted conditions. In theory, food intake would increase retention time in the stomach, leading to prolonged dissolution and improved absorption. In addition, the intestinal solubility and absorption of TQ may increase in the presence of bile salts that are secreted following the food intake. These effects are unlikely to be formulation dependent, as both the capsule and tablet have fast and comparable in-vitro dissolution profiles (b) (4) for both formulations). Thus, it is reasonable to assume that food would exert similar effect on the to-be marketed tablet formulation as the capsule studied herein. Furthermore, TQ tablets were efficacious when administered with food in the Phase 3 trials. Therefore, TQ is recommended to be administered with food.

Drug-Drug Interactions (DDIs)

Effect of TQ on the PK of Other Agents

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

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

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

	OCT2	MATE1	MATE2-K
Mean IC_{50} (μM)	0.282	1.99	0.632
Mean IC_{50} -C (μM)[a]	0.0419	0.435	0.170
$C_{max,u}/IC_{50}$-C ratios[b]	0.16	0.015	0.038

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

[b]: The Applicant reported a 99.5% protein binding of TQ; the unbound fraction of TQ in plasma (fu,p) was set to 1% (fu,p = 0.01) if protein binding was experimentally determined to be < 1% per the in vitro DDI draft guidance; to calculate Cmax in μM, mean Cmax ≈ 330 ng/mL, MW=463.5 g/mol as free base

As shown in Table 16, after correcting for nonspecific binding of TQ to the assay plate, the corrected $C_{max,u}/IC_{50}$ ratios using the adjusted lower IC_{50} values are either close to or slightly higher than the guidance recommended cutoff values (0.1 for OCT2 and 0.02 for MATEs). In addition, TQ at 300 mg single dose was associated with small reversible increases in serum creatinine without impacting the kidney function (Studies 200951, TAF114582). Since the active tubular secretion of creatinine is mediated by renal transporters including OCT2 and MATEs, the observed increase in serum creatinine following the TQ treatment is indicative of the inhibitory effect of TQ on renal transporters of OCT2 and/or MATEs. The review team recommends that coadministration of TQ with OCT2 and MATE substrates (e.g., dofetilide, metformin) should be avoided.

Other anti-malarial drugs: Clinical studies were conducted to evaluate the impact of TQ on the PK of other anti-malarial drugs including CQ (Study TAF106491) and ACTs, i.e., dihydroartemisinin/piperaquine (DHA/PQP) or artemether/lumefantrine (AL) (Study 200951). Results from these studies demonstrated that TQ has no clinically relevant impact on the systemic exposure of these anti-malarial drugs and therefore no dose adjustment is deemed necessary for CQ or ACTs when administered with TQ.

Effect of Other Agents on the PK of TQ

Effect on metabolism of TQ: It is unlikely that metabolism of TQ will be affected by other drugs since TQ undergoes slow and negligible metabolism as evidenced in in vitro hepatocyte and microsomal studies (Study 2014N210919).

TQ as a potential substrate of P-gp transporter: An in vitro study was conducted to evaluate if TQ is a substrate of P-gp transporter (Study 2017N327858). No conclusion can be made from this study due to high non-specific binding of TQ to the test system. However, the safety risk associated with potential increase of TQ exposure when coadministered with strong Pgp inhibitor(s) is expected to be low because of acceptable safety profiles of TQ observed at the supratherapeutic dose of 1200 mg (400 mg once daily for 3 days) (Study TAF114582 and Study SB252263/015).

TQ as a potential substrate of renal and/or hepatic transporters: TQ is unlikely a substrate of renal transporters, since kidney is not identified as the major elimination organ for TQ based on

the currently available data (Study RSD-101GZN). In addition, the Applicant proposed that TQ is unlikely a substrate of hepatic uptake transporters of OATP1B1 and OATP1B3 based on the tissue distribution data from quantitative whole body autoradiography (QWBA) study in rats. A hepatic Kp ratio (the ratio of Kp in the liver to that in other tissues) that was calculated from QWBA tissue distribution data was proposed to be an index of liver-specific distribution (Mikkaichi et al, 2015). A hepatic Kp ratio <10 was proposed as a threshold for excluding the involvement of OATP in vivo (Mikkaichi et al, 2015). The Applicant reported that the hepatic Kp values calculated from the QWBA data are all lower than 10, suggesting that TQ is not an OATP substrate. Furthermore, TQ succinate, a weak base, exists largely as an organic cation at physiological pH, which further supports that TQ is unlikely a substrate of hepatic uptake transporters of OATP1B1 and OATP1B3.

Effect of other anti-malarial drugs: Results from the clinical DDI study (Study TAF106491) showed that coadministration of CQ increased TQ C_{max} and $AUC_{0\text{-}24h}$ at 300 mg by 38% and 24%, respectively, with little impact on the overall TQ exposure ($AUC_{0\text{-}\infty}$ and $t_{1/2}$). Similarly, coadministration of DHA/PQP increased TQ C_{max} at 300 mg by 38% (Study 200951). Given the acceptable safety profile of TQ at doses up to 1200 mg (400 mg once daily for 3 days) (Study TAF114582), these changes in TQ exposure are not considered to be clinically significant. In addition, there was no change in TQ exposure when administered concomitantly with AL. Therefore, the review team agrees that TQ can be co-administered with other anti-malarial drugs such as CQ or ACTs without dose adjustment.

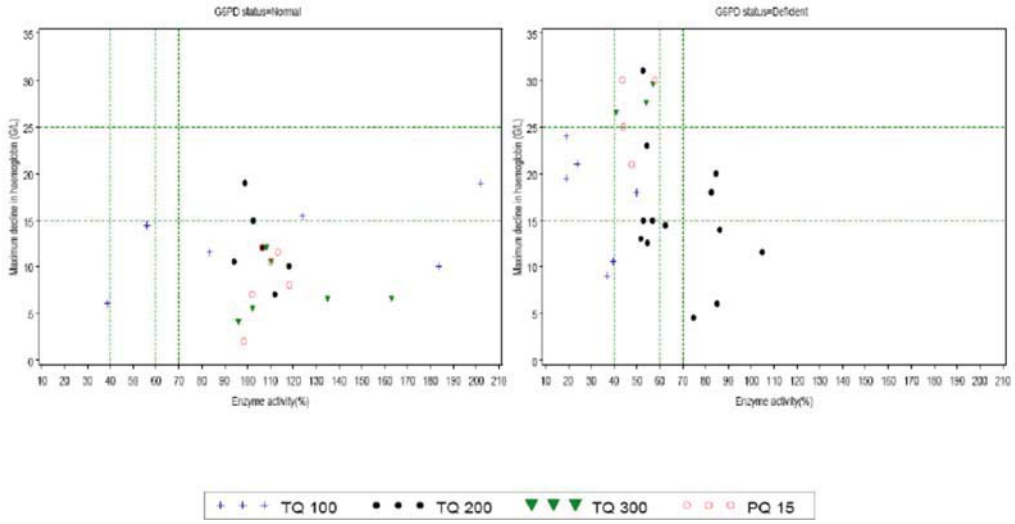
Effect of gastric acid–reducing agents (ARAs): TQ is a weak base and displays pH-dependent solubility in the physiologically relevant condition. Therefore, co-administration with a gastric ARA may alter the absorption of TQ. No clinical study has been conducted to assess the effect of gastric ARAs on the PK of TQ. TQ is proposed to be administered with food. The solubility of TQ in the fed state simulated intestinal fluid (FeSSIF) (1.05 mg/mL) is much higher than that in the fasted state simulated intestinal fluid (FeSSIF) (0.01 mg/mL) at pH 6.5 and is close to the intestinal luminal concentration of TQ calculated as the dose/250 mL (1.2 mg/mL). In addition, several case studies reported that food intake mitigated the impact of ARAs (proton-pump inhibitors and histamine-2 receptor antagonists) on the exposures of week base drugs (Sun W et al, 2017; Ware JA, 2013). Based on the above evidence, the review team considers that the risk of pH-mediated drug-drug interaction is low for TQ.

5. ***Should a cut-off (<70% G6PD enzyme activity of normal) to refer to G6PD deficiency as proposed by the sponsor be included in labeling?***

The applicant evaluated the hemolytic potential of 100 mg, 200 mg, and 300 mg TQ in G6PD-deficient heterozygous females (WHO-class III variant) to G6PD-normal subjects in Study TAF110027. G6PD enzyme activity was determined using cytochemical staining in the 100mg cohorts and a quantitative assay (with a locally defined median as benchmark for 100% normal activity as determined in study TAF115016*)* was used to enroll subsequent TQ dose cohorts. The applicant reports that subjects with enzyme activity ≥70% in the G6PD deficient and G6PD normal TQ 200 mg groups had similar median decline in hemoglobin. This study appears to be

the source of the >70% enzyme activity cut-off enrollment criteria for subsequent studies and the applicant's proposal to withhold TQ from patients with G6PD enzyme levels <70% of normal.

A review of literature illustrates broadly-cited, enzyme activity in WHO-defined G6PD deficiency categories. Mild to moderate deficiency is defined as 10-60% of normal enzyme activity, severe deficiency as < 10% of normal enzyme activity, and enzyme activity between 60-150 % of normal enzyme activity is classified as normal functional status. The application of <70% enzyme activity to withhold TQ treatment essentially rests with one subject as the applicant enrolled 2 subjects in the 60-80% deficient cohort, one of whom had enzyme activity > 70% and the other with enzyme activity < 70%.



Source: Applicant's study report of TAF110027

Figure 4: Maximum Decline in Hemoglobin up to Day 14 and baseline Enzyme Activity by G6PD Status

Reviewer's comment: The Applicant did not provide sufficient evidence to support inclusion of the proposed cut-off for G6PD enzyme activity in labeling, particularly given that the cut-off differs from the prevalent threshold cited in the literature. Defining G6PD deficiency in the label with the < 70% enzyme activity cut-off without reference to a specific quantitative test may warrant considerations of G6PD assay performance and validation, which have not been addressed by the Applicant. It is the recommendation of the reviewer that the <70% of normal enzyme activity cut-off proposed in the warning section of the proposed labeling should be removed and, where applicable, reference should be made to G6PD-deficient patients only.

7 Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Trials

A list of the relevant clinical trials of this NDA is included in the following table. Three clinical trials, TAF112582 Part 1 and Part 2 and TAF116564, are multicenter, double-blind, double-dummy, randomized, controlled trials to support the efficacy and safety of TQ. The two parts of TAF112582 were conducted and assessed independently and are considered as two separate trials for this review.

CQ was used to treat the blood-stage malaria infection in all subjects in all three trials. It does not have any activity in preventing the relapse of liver-stage hypnozoites. CQ monotherapy was a randomized arm in TAF112582 Part 1 and Part 2 and is considered a placebo arm as the proposed indication is for the radical cure (prevention of relapse) of *P. vivax* malaria. In TAF116564, there was no CQ alone group. The active control group was PQ given with CQ; the primary endpoint was safety and efficacy was a secondary endpoint.

Table 17. Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
TAF112582 Part 1	Multicenter, double-blind, double-dummy, randomized, placebo- and active-controlled	TQ 50 mg, TQ 100 mg, TQ 300 mg, TQ 600 mg, PQ, CQ alone. All groups with CQ (Day 1 to 3). Oral route.	Recurrence-free efficacy at 6 months	15 days/6 months	Randomized 55 57 57 56 50 54	Positive Giemsa smear for *P. vivax* Parasite density >100/µL and <100,000/µL	7 centers 4 countries
TAF112582 Part 2	Multicenter, double-blind, double-dummy, randomized, placebo- and active-controlled	CQ (Day 1 to 3) + 300 mg TQ single dose (Day 1 or 2) CQ (Day 1 to 3) + 15 mg PQ once daily from Day 2 for 14 days CQ alone regimen (Day 1 to 3) Oral route.	Recurrence-free efficacy at 6 months	15 days/6 months	Randomized 260 129 133	Positive malarial smear for *P. vivax*. Parasite density of >100 and <100,000/µL.	8 centers 6 countries
TAF116564	Multicenter, double-blind, double-dummy, randomized, active-controlled	CQ (Day 1 to 3) + 300 mg TQ single dose (Day 1 or 2) CQ (Day 1 to 3) + 15 mg PQ once daily from Day 1 or 2 for 14 days Oral route.	Recurrence-free efficacy at 6 months	15 days/6 months	166 85	Positive malarial smear for *P. vivax.* Parasite density of >100 and <100,000/µL.	7 centers 5 countries
Studies to Support Safety							
TAF114582	Phase 1, randomized, placebo controlled, thorough QT study in healthy volunteers	TQ 300mg, 600mg, 1200mg; moxifloxacin 400mg	QT duration corrected for heart rate by Fridericia's formula (QTcF).	3 days/ 13 weeks	260	Adult healthy subjects	2 centers in the USA
201807	Phase 1 ophthalmic safety study in healthy volunteers	TQ 300mg single dose	Proportion of subjects with retinal changes from baseline	1 day / 90 days	300	Adult healthy subjects	3 centers in USA

7.1.2. Review Strategy

Data Sources

This NDA was submitted in eCTD format. Data sources include protocols, reporting and analysis plans, study reports, integrated summaries of efficacy and safety, and data sets (in both Study Data Tabulation Module (SDTM) and Analysis Data Model (ADaM) formats). Data sets and software code are available at \\Cdsesub1\evsprod\NDA210795\0000\m5\datasets.

Data and Analysis Quality

Overall, the quality of data and analysis was adequate. It is possible to reproduce the primary analysis endpoint from the original data source. Blinding/un-blinding procedures were generally well documented. Quality control/assurance procedures were documented. Statistical analysis plans were finalized before un-blinding.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Study TAF112582 Part 1

Trial Objectives

The primary objective of trial TAF112582 Part 1 was to determine the efficacy of TQ given with CQ as a radical cure for *P. vivax* malaria, compared to a CQ alone control.

Secondary objectives included:

- To assess the safety and tolerability of TQ when administered to subjects with *P. vivax* malaria
- To characterize the population pharmacokinetics of TQ in the subjects with *P. vivax* malaria
- To explore potential PK/pharmacodynamic (PD) relationships (if data permitted)

Trial Design and Endpoints

TAF112582 was a multi-center, double-blind, double-dummy, parallel-group, randomized, active-controlled study conducted in two parts. Part 1 (dose ranging) is presented in this section. The optimal TQ dose level from Part 1 was investigated further in the second part of the study (Part 2), discussed in the next section of this review. Each part of the study represented a distinct and independent study.

Considering that subjects with higher parasite loads at baseline might have higher relapse rates, stratified randomization was performed by baseline parasite count (≤7500/µL and >7500/µL). Eligible subjects were randomized to one of the following 6 groups:

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

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

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

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

Key Inclusion and Exclusion Criteria

Inclusion criteria

Inclusion criteria included, but were not limited to:

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

Exclusion criteria

Exclusion criteria included, but were not limited to:

1. Mixed malaria infections (e.g., identified by Giemsa-stained smear or rapid diagnostic test)
2. Severe *P. vivax* malaria as defined by World Health Organization (WHO) criteria
3. Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency, assessed by a quantitative spectrophotometric phenotype assay:
   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 Hemoglobin (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.

Statistical Analysis Plan

Analysis Populations

Intent to Treat (ITT) Population: all randomized subjects who received at least one dose of study medication, and who had at least one *P. vivax* parasite assessment after randomization. Subjects were analyzed according to their randomized treatment. This population was the primary population for all efficacy analyses.

Comment: We do not agree with this definition, because post-randomization/post-treatment information was used as an exclusion for this population, which might be related to the assigned treatment and lead to differences in patient populations across arms. However, all randomized subjects were included in the ITT population with no exclusions due to not having parasite assessment after randomization. Therefore, the analysis based on the ITT population is acceptable.

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

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

Comment: As both mITT and PP populations were defined using post-randomization/post-treatment information (such as taking a concomitant medication with an anti-malarial activity between Day 1 and Day 180 as a major protocol violation), the interpretations of the analysis results from these populations should be made with caution.

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

Analysis Methods

The proportion of subjects with recurrence-free efficacy at 6 months was summarized by treatment group for the ITT (primary analysis), mITT, and PP populations. For the primary analysis, recurrence-free efficacy at 6 months was analyzed using Kaplan-Meier method.

Subjects who did not relapse would be censored at the time of last available smear. The planned Kaplan-Meier analysis assumed non-informative censoring, which assumes that the censoring was unrelated to study treatment. We conducted an additional analysis that treated early censored subjects as treatment failures as a sensitivity analysis.

Treatment efficacy at 6 months was compared between a TQ group and the CQ alone group using a log-rank test with a two-sided 5% significance level.

To control the possible inflation of the type I error due to multiple treatment arms, a closed testing approach was adopted, i.e., no adjustment for each hypothesis test was considered, but hypotheses were tested in order. Each of the four TQ groups against the CQ alone group was tested in a step-down approach, starting with the highest dose. As soon as a dose was not found to be statistically significantly better than CQ alone, testing stopped.

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

Protocol Amendments

Three amendments were made. In Amendment 1, a blood smear for parasitological assessment 6 to 12 hours after the first smear was obtained on Days 1 to 3 was added. Other amendments would not affect the assessment of efficacy.

Compliance with Good Clinical Practices

This study was performed in compliance with Good Clinical Practices.

Financial Disclosure

There were no financial interests to disclose.

Patient Disposition

This study was conducted from 9/19/2011 to 3/25/2013 in 8 centers in Brazil, India, Peru, and Thailand. A total of 329 subjects were randomized, all were included in the ITT population, 319 (97%) completed the study, and 10 subjects were withdrawn due to loss to follow-up. All except for 3 subjects, who met QTc withdrawal criteria, completed study medication, as shown in the following table.

Following unblinding, India was considered to have an inadequate background relapse rate of 10% in the CQ group and, therefore, 57 subjects from India were excluded from the mITT population.

Comment: As stated above, the exclusion of a geographical region demonstrating a level of

relapse in the CQ alone group which was inadequate for demonstrating a potential treatment effect was included in the Reporting and Analysis Plan. However, the exact inadequate level should have been clearly defined in the Reporting and Analysis Plan prior to unblinding in order to avoid the possibility of bias being introduced into the decision. It appears to have been defined after un-blinding. However, the mITT population was not the primary analysis population for efficacy, so, this exclusion does not affect the primary efficacy analysis.

Table 18. TAF112582 Part 1: Patient Disposition

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

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

Protocol Violations/Deviations

Forty-one subjects in the mITT population were excluded from the PP population. Protocol deviations included violations of assessment procedures, visit schedule, biological specimen sample procedures, prohibited medication or device, withdrawal criteria, etc. The distributions were well-balanced (Table 18).

Demographic Characteristics

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

Table 19. TAF112582 Part 1: Demographic characteristics (ITT population)

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

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

The following table shows other baseline characteristics, including G6PD enzyme activity, malarial signs and symptoms, splenomegaly, previous malarial episode, and *P. vivax* parasite counts. The treatment groups were well-balanced by these baseline characteristics.

Table 20. TAF112582 Part 1: Other baseline characteristics (ITT population)

	CQ alone (N=54)	CQ+TQ 50 mg (N=55)	CQ+TQ 100 mg (N=57)	CQ+TQ 300 mg (N=57)	CQ+TQ 600 mg (N=56)	CQ+PQ (N=50)
G6PD enzyme activity (IUg/Hb)						
Mean	9.2	9.9	9.4	9.2	9.4	9.5
SD	2.49	2.98	2.89	2.36	2.65	2.55
Median	8.7	9.1	8.9	8.6	8.8	9.0
Range	5, 17	6, 18	6, 19	4, 15	5, 18	5, 16
Abdominal pain, n (%)						
Absent	36 (67)	36 (65)	35 (61)	40 (70)	37 (66)	26 (52)
Mild	16 (30)	16 (29)	16 (28)	13 (23)	18 (32)	19 (38)
Moderate	1 (2)	1 (2)	5 (9)	3 (5)	0	4 (8)
Severe	1 (2)	2 (4)	1 (2)	1 (2)	1 (2)	1 (2)
Anorexia, n (%)						
Absent	29 (54)	32 (58)	29 (51)	38 (67)	33 (59)	16 (32)
Mild	21 (39)	18 (33)	20 (35)	16 (28)	18 (32)	24 (48)
Moderate	4 (7)	5 (9)	7 (12)	2 (4)	5 (9)	9 (18)
Severe	0	0	1 (2)	1 (2)	0	1 (2)
Chills and rigors, n (%)						
Absent	7 (13)	1 (2)	4 (7)	5 (9)	5 (9)	2 (4)
Mild	18 (33)	23 (42)	22 (39)	24 (42)	22 (39)	24 (48)
Moderate	15 (28)	17 (31)	12 (21)	15 (26)	13 (23)	14 (28)
Severe	14 (26)	14 (25)	19 (33)	13 (23)	16 (29)	10 (20)
Coughing, n (%)						
Absent	45 (83)	50 (91)	51 (89)	54 (95)	54 (96)	41 (82)
Mild	9 (17)	5 (9)	6 (11)	3 (5)	2 (4)	9 (18)
Diarrhea, n (%)						
Absent	49 (91)	53 (96)	53 (93)	52 (91)	50 (89)	45 (90)
Mild	3 (6)	1 (2)	3 (5)	5 (9)	5 (9)	4 (8)
Moderate	2 (4)	1 (2)	1 (2)	0	1 (2)	1 (2)
Severe	0	0	0	0	0	0
Dizziness, n (%)						
Absent	27 (50)	26 (47)	32 (56)	33 (58)	31 (55)	24 (48)
Mild	22 (41)	28 (51)	19 (33)	23 (40)	22 (39)	21 (42)
Moderate	3 (6)	1 (2)	6 (11)	0	1 (2)	5 (10)
Severe	2 (4)	0	0	1 (2)	2 (4)	0
Headache, n (%)						
Absent	6 (11)	6 (11)	4 (7)	8 (14)	4 (7)	7 (14)
Mild	23 (43)	22 (40)	26 (46)	22 (39)	24 (43)	16 (32)
Moderate	10 (19)	11 (20)	7 (12)	13 (23)	13 (23)	12 (24)
Severe	15 (28)	16 (29)	20 (35)	14 (25)	15 (27)	15 (30)
Nausea, n (%)						
Absent	31 (57)	29 (53)	23 (40)	33 (58)	29 (52)	28 (56)
Mild	18 (33)	24 (44)	28 (49)	21 (37)	23 (41)	20 (40)
Moderate	5 (9)	2 (4)	6 (11)	2 (4)	3 (5)	1 (2)

	CQ alone (N=54)	CQ+TQ 50 mg (N=55)	CQ+TQ 100 mg (N=57)	CQ+TQ 300 mg (N=57)	CQ+TQ 600 mg (N=56)	CQ+PQ (N=50)
Severe	0	0	0	1 (2)	1 (2)	1 (2)
Vomiting, n (%)						
Absent	47 (87)	47 (85)	44 (77)	47 (82)	46 (82)	39 (78)
Mild	4 (7)	6 (11)	8 (14)	9 (16)	8 (14)	8 (16)
Moderate	3 (6)	2 (4)	5 (9)	1 (2)	2 (4)	3 (6)
Severe	0	0	0	0	0	0
Pruritus/itching, n (%)						
Absent	50 (93)	50 (91)	52 (91)	54 (95)	52 (93)	45 (90)
Mild	4 (7)	5 (9)	2 (4)	3 (5)	4 (7)	4 (8)
Moderate	0	0	3 (5)	0	0	1 (2)
Severe	0	0	0	0	0	0
Splenomegaly, n (%)						
Yes	1 (2)	2 (4)	3 (5)	4 (7)	5 (9)	2 (4)
No	53 (98)	53 (96)	54 (95)	53 (93)	51 (91)	48 (96)
Previous malarial episode, n (%)						
Yes	33 (61)	35 (64)	36 (63)	28 (49)	31 (55)	31 (62)
No	21 (39)	20 (36)	20 (35)	27 (47)	25 (45)	18 (36)
Unknown	0	0	1 (2)	2 (4)	0	1 (2)
***P. vivax* - asexual parasite count, n (%)**						
≤7500/µL	37 (69)	38 (69)	41 (72)	37 (65)	35 (63)	36 (72)
>7500/µL	17 (31)	17 (31)	16 (28)	20 (35)	21 (38)	14 (28)
Subjects with gametocytes, n (%)						
Yes	41 (76)	41 (75)	44 (77)	47 (82)	44 (79)	36 (72)
***P. vivax* - gametocyte parasite count per µL**						
Mean (SD)	41 (76)	41 (75)	44 (77)	47 (82)	44 (79)	36 (72)
Median	149	160	77.0	138	141	106
Range	0, 3000	0, 3500	0, 7275	0, 4378	0, 8175	0, 9046

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The following table shows treatment compliance, which was high and comparable for all groups.

Table 21. TAF112582 Part 1: Treatment Compliance (ITT population)

	CQ alone (N=54)	CQ+TQ 50 mg (N=55)	CQ+TQ 100 mg (N=57)	CQ+TQ 300 mg (N=57)	CQ+TQ 600 mg (N=56)	CQ+PQ (N=50)
Number of compliant doses of CQ, n (%)						
1	0	0	0	0	0	0
2	0	1 (2)	0	0	0	1 (2)
3	54 (100)	54 (98)	57 (100)	57 (100)	56 (100)	49 (98)
Compliant with TQ/TQ placebo dosing, n (%)						
Yes	54 (100)	55 (100)	57 (100)	55 (96)	56 (100)	50 (100)
No	0	0	0	2 (4)	0	0
Compliance with PQ/PQ placebo dosing on Day 2, n (%)						
Yes	54 (100)	55 (100)	57 (100)	57 (100)	56 (100)	49 (98)

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

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

Source: Table 21, Study Report

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

Efficacy Results – Primary Endpoint

Relapse-Free Efficacy at 6 Months (Kaplan-Meier Approach)

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

Table 22. TAF112582 Part 1: Relapse-free efficacy at 6 months (ITT population)

	CQ alone (N=54)	CQ+TQ 50 mg (N=55)	CQ+TQ 100 mg (N=57)	CQ+TQ 300 mg (N=57)	CQ+TQ 600 mg (N=56)	CQ+PQ (N=50)
Number of Subjects, n(%)						
Relapse-free efficacy at 6 months	21 (39)	29 (53)	29 (51)	48 (84)	43 (77)	34 (68)
Relapse prior to Study Day 180	31 (57)	22 (40)	25 (44)	6 (11)	4 (7)	12 (24)
Censored, prior to 6 months [a]	2 (4)	4 (7)	3 (5)	3 (5)	9 (16)	4 (8)
Taking a drug with anti-malarial action in first 6 months (and not parasitemic)	1	3	1	1	4	2
No asexual P. vivax parasites at baseline	0	0	1	0	0	0
No assessment at 6 months	1	1	1	2	5	2
Relapse-free efficacy rate at 6 months, %						

	CQ alone (N=54)	CQ+TQ 50 mg (N=55)	CQ+TQ 100 mg (N=57)	CQ+TQ 300 mg (N=57)	CQ+TQ 600 mg (N=56)	CQ+PQ (N=50)
Estimate	37.5	57.7	54.1	89.2	91.9	77.3
95% CI	23,52	43,70	40,66	77,95	80,97	63,87
Difference from CQ at 6 months, %						
Estimated difference		20.3	16.6	51.7	54.5	39.9
95% CI		0,40	-3,36	35,69	38,71	21,59
Log rank test p-value[b]		0.048[c]	0.158	<0.0001	<0.0001	0.0004

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

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

Table 23. TAF112582 Part 1: Efficacy results (categorical) at 6 months (ITT population)

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

The analysis results in the mITT and PP populations also demonstrated that the 300- and 600-mg TQ groups achieved significantly higher relapse-free efficacy results compared with the control group. A more traditional micro-ITT analysis where subjects without baseline pathogen excluded also would produce similar results given that only one subject did not have *P. vivax* at baseline.

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

Gender, Race, Age, Weight, Body Mass Index, Country, and Baseline Parasite Count Stratum

The following table shows results of the subgroup analyses, most of which show results similar to the overall study results. It is difficult to make conclusions for age, as the numbers of subjects who were 65 years or older were too small. The treatment effects were similar in male and females. It is important to consider race along with geographic region since all Asians were from India and Thailand and, as noted previously, the CQ-alone rate in India was high, reducing the treatment effect of TQ. It appeared that the treatment effect varied by body weight, but this could also have been related to geographic region and race. The numbers of subjects with a BMI ≥ 30 were too small to make a conclusion.

Table 24. TAF112582 Part 1: Relapse-free efficacy at 6 months (ITT population) by age, sex, race, weight, body mass index, country, and baseline parasite count

n/N (%)	CQ alone (N=54)	CQ+TQ 50 mg (N=55)	CQ+TQ 100 mg (N=57)	CQ+TQ 300 mg (N=57)	CQ+TQ 600 mg (N=56)	CQ+PQ (N=50)
Age (yrs)						
<65	20/53 (37.7)	28/54 (51.9)	29/55 (52.7)	48/57(84.2)	41/53(77.4)	33/48(68.8)
≥65	1/1 (100)	1/1 (100.0)	0/2	0	2/3 (66.7)	1/2 (50)
Sex						
Male	17/39 (43.6)	18/37 (48.7)	21/44 (47.7)	37/43 (86.1)	34/45(75.6)	25/35(71.4)
Female	4/15 (26.7)	11/18 (61.1)	8/13 (61.5)	11/14 (78.6)	9/11(81.8)	9/15(60.0)
Race						
American Indian or Alaska Native*	4/27 (14.8)	10/27 (37.0)	10/28 (35.7)	21/29 (72.4)	19/29(65.5)	14/25(56.0)
Asian	17/26 (65.4)	19/27 (70.4)	18/27 (66.7)	27/28 (96.4)	23/26(88.5)	19/22(86.4)
Multiple	0/1	0/1	1/2 (50)	0	1/1(100)	1/3(33.3)
Weight (kg)						
<60	14/30 (46.7)	16/33 (48.5)	18/35 (51.4)	26/30 (86.7)	19/27(70.4)	18/26(69.2)
≥60	7/24 (29.2)	13/22 (59.1)	11/22 (50.0)	22/27 (81.5)	24/29(82.8)	16/24(66.7)
Body Mass Index (kg/m^2)						
<30	19/50 (38.0)	27/48 (56.3)	26/52 (50.0)	46/54 (85.2)	39/50 (78.0)	31/44 (70.5)
≥30	2/4 (50.0)	2/7 (28.6)	3/5 (60.0)	2/3 (66.7)	4/6 (66.7)	3/6 (50.0)
Country						
Brazil	1/6(16.7)	1/6(16.7)	2/6(33.3)	5/6(83.3)	6/7(85.7)	4/6(66.7)
India	9/10(90.0)	10/11(90.9)	8/11(72.7)	9/9(100.0)	10/10(100)	6/6(100.0)
Peru	3/22(13.6)	9/22(40.9)	9/24(37.5)	16/23(69.6)	14/23(60.9)	11/22(50.0)
Thailand	8/16(50.0)	9/16(56.3)	10/16(62.5)	18/19(94.7)	13/16(81.3)	13/16(81.3)
Baseline parasite count (/µL)						

n/N (%)	CQ alone (N=54)	CQ+TQ 50 mg (N=55)	CQ+TQ 100 mg (N=57)	CQ+TQ 300 mg (N=57)	CQ+TQ 600 mg (N=56)	CQ+PQ (N=50)
≤7500	14/37(37.8)	21/40(52.5)	19/39(48.7)	32/39(82.1)	32/38(84.2)	26/36(72.2)
>7500	7/17(41.2)	8/15(53.3)	10/18(55.6)	16/18(88.9)	11/18(61.1)	8/14(57.1)

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

Conclusions

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

7.2.2.Study TAF112582 Part 2

Trial Objective

The primary efficacy objective was to determine the efficacy of TQ given with CQ as a radical cure for *P. vivax* malaria relative to CQ alone.

Trial Design and Endpoints

This study was a Phase 3, randomized, double-blind, double-dummy, active-controlled trial of the effectiveness and safety of TQ (300 mg).

Eligible subjects were randomized 2:1:1 at each center to one of the three treatment arms:

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

All subjects received the same number of tablets/capsules for 15 days for blinding purposes. Subjects stayed in the clinic and received directly observed therapy from Days 1 to 3 or until parasite clearance was confirmed. All patients received a 3-day course of CQ which was expected to clear the initial blood stage infection. The CQ+PQ arm was included to provide a concurrent benchmark. The Applicant states that CQ, with or without PQ, is the standard of care for the treatment of *P. vivax* malaria in most endemic countries. Study visits included Days 1, 2, and 3, 5, 8, 11, 15, 22, 29, 60, 90, 120, 150, and 180.

Primary Efficacy Endpoint

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

- Subject had a non-zero *P. vivax* asexual parasite count at baseline.

- Subject demonstrated initial clearance of *P. vivax* parasitemia. This was defined as 2 negative asexual *P. vivax* parasite counts, with at least 6 hours between counts, and no positive counts in the interval.
- Subject had no positive asexual *P. vivax* parasite count at any assessment prior to or on Day 201 following initial parasite clearance.
- Subject did not take a concomitant medication with antimalarial activity at any point between Day 1 and the last parasite assessment.
- Subject was parasite-free at 6 months. This was defined as a negative asexual *P. vivax* parasite count at the first parasite assessment performed on or after Day 166.

Subjects with no asexual *P. vivax* parasites at baseline were censored with time to recurrence = 0 days. Subjects who did not have initial clearance of *P. vivax* were censored with time to recurrence = 0 days. Subjects who had a positive count prior to or on Day 201 following initial parasite clearance were classified as recurrences, with time to recurrence = (date of first positive count) – (date of Day 1) days. Subjects who received a drug with antimalarial activity, but never had a positive asexual *P. vivax* parasite count after initial clearance were censored.

Comment: We do not agree with censoring those subjects who did not have initial clearance of P. vivax as it is possible that randomized treatment could have affected the initial clearance. However, we agree with excluding those subjects with no asexual P. vivax parasites at baseline from the primary analysis.

Secondary Efficacy Endpoints

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

Key Inclusion and Exclusion Criteria

Inclusion criteria

Inclusion criteria included, but were not limited to:

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

Exclusion criteria

Exclusion criteria included, but were not limited to:

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

Statistical Analysis Plan

Analysis Populations

***Microbiologic intent-to-treat population (micro-ITT)*:** All randomized subjects who received at least 1 dose of study medication, who had at least one *P. vivax* parasite assessment after randomization, and who had a positive parasite smear for *P. vivax* at baseline. Subjects were analyzed according to their randomized treatment. This population was the primary population for all efficacy analyses in Part 2 of the study.

Comment: This is the primary analysis population. We usually do not exclude subjects for not having post-randomization outcome assessment. However, in this study no subjects were excluded for this reason. Therefore, using the Micro-ITT population in the primary efficacy analysis is acceptable.

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

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

Analysis Methods

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

Comment: The assumption for censoring in the Cox proportional hazards model was non-informative, meaning that the censoring was not related to treatment. This is likely not true in clinical trials. The logistic regression analysis assumes missing=failure and may be more appropriate. We will conduct an additional more conservative analysis by assuming missing=failure in the TQ group and missing=success in the control group. If this extreme case continues to show the efficacy of TQ then we can feel confident that missing data does not impact the overall conclusions of the study.

Study Results

Compliance with Good Clinical Practices

The study was performed in compliance with Good Clinical Practices.

Financial Disclosure

There were no financial interests to disclose.

Patient Disposition

This study was conducted between 4/24/2014 and 11/18/2016 in 8 centers in Brazil, Ethiopia, Cambodia, Peru, Philippines, and Thailand. The following table shows patient disposition in TAF112582 Part 2. All randomized subjects were included in the micro-ITT population. The majority of the subjects (96%) completed the study. Reasons for discontinuation were well-balanced.

Table 25. TAF112582 Part 2: Patient disposition

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

[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.
Source: Tables 7 and 10, Study Report

Protocol Violations/Deviations

As the previous table shows, 78% of the subjects were included in the PP Population.
Protocol deviations with any potential impact on the validity, accuracy, or completeness of data were considered as important by the Applicant. Important protocol deviations are tabulated in the following table. Protocol violations/deviations were balanced among the three treatment groups.

Table 26. TAF112582 Part 2: Protocol violations/deviations

Category/Coded Term	CQ alone (N=133) n (%)	CQ+TQ (N=260) n (%)	CQ+PQ (N=129) n (%)
Assessments and/or procedure	46 (35)	95 (37)	40 (31)
Failure to comply with dosing procedure	24 (18)	49 (19)	20 (16)

Category/Coded Term	CQ alone (N=133) n (%)	CQ+TQ (N=260) n (%)	CQ+PQ (N=129) n (%)
Failure to report SAE, pregnancy, or liver function abnormalities per protocol	1 (<1)	3 (1)	1 (<1)
Informed consent process	3 (2)	6 (2)	3 (2)
Missed assessment or procedure	18 (14)	38 (15)	17 (13)
Other	15 (11)	24 (9)	13 (10)
Randomization procedure (e.g., subject assigned to wrong stratum, subject randomized out of order)	0	4 (2)	0
Failure to comply with dosing procedure	24 (18)	49 (19)	20 (16)
Eligibility criteria not met	0	4 (2)	1 (<1)
Not withdrawn after developing withdrawal criteria	0	1 (<1)	1 (<1)
Other protocol deviation category	2 (2)	4 (2)	3 (2)
Prohibited medication or device	11 (8)	20 (8)	5 (4)
Received wrong treatment or incorrect dose	2 (2)	3 (1)	0
Visit, assessment, or time point window	24 (18)	52 (20)	26 (20)
Other	3 (2)	4 (2)	3 (2)
Out of window – efficacy assessment	16 (12)	40 (15)	21 (16)
Out of window – PK collection	0	2 (<1)	1 (<1)
Out of window – Safety assessment	6 (5)	12 (5)	4 (3)

Source: Table 9, Study Report

Demographic Characteristics

Demographic characteristics are presented in the following table. The majority of the subjects were male. Only 2.3% of the subjects were 65 years old or older. American Indians or mixed (multiple) races accounted for 69% of the subjects. Brazil, Philippines, and Thailand were the three countries that enrolled the most subjects.

Table 27. TAF112582 Part 2: Demographic characteristics

	CQ alone (N=133)	CQ+TQ (N=260)	CQ+PQ (N=129)
Sex, n(%)			
Male	97 (73)	196 (75)	99 (77)
Female	36 (27)	64 (25)	30 (23)
Age in years			
Mean (SD)	35.3 (14.2)	35.0 (14.4)	34.7 (14.3)
Median	31.0	31.5	33.0
Min, max	17.0, 71.0	15.0, 79.0	15.0, 66.0
Age group, n(%)			
< 65 years	131 (98.5)	253 (97.3)	126 (97.7)
≥ 65 years	2 (1.5)	7 (2.7)	3 (2.3)
Race, n(%)			
American Indian or Alaska native	43 (32)	81 (31)	41 (32)
Asian - Southeast Asian heritage	26 (20)	50 (19)	26 (20)

	CQ alone (N=133)	CQ+TQ (N=260)	CQ+PQ (N=129)
Black or African American	14 (11)	28 (11)	13 (10)
Multiple	47 (35)	97 (37)	47 (36)
White	3 (2)	4 (2)	2 (2)
Ethnicity, n (%)			
Hispanic or Latino	93 (69.9)	182 (70.0)	89 (69.0)
Not Hispanic or Latino	40 (30.1)	78 (30.0)	40 (31.0)
Country, n (%)			
Brazil	53 (39.8)	105 (40.4)	52 (40.3)
Ethiopia	14 (10.5)	28 (10.8)	13 (10.1)
Cambodia	10 (7.5)	19 (7.3)	9 (7.0)
Peru	40 (30.1)	77 (29.6)	38 (29.5)
Philippines	1 (0.8)	3 (1.2)	2 (1.6)
Thailand	15 (11.3)	28 (10.8)	15 (11.6)

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

Other baseline characteristics, such as G6PD enzyme activity, malarial signs and symptoms, splenomegaly, previous malarial episode, and *P. vivax* parasite counts, were well balanced in the three treatment groups.

Table 28. TAF112582 Part 2: Other baseline characteristics, including malarial signs and symptoms, splenomegaly, previous malarial episode, and *P. vivax* parasite counts (micro-ITT population)

Baseline risk Factor / Disease Characteristics	CQ alone (N=133)	CQ+TQ (N=260)	CQ+PQ (N=129)
G6PD enzyme activity (IUg/Hb)			
Mean (SD)	8.4 (1.3)	8.5 (1.5)	8.6 (1.2)
Median	8.2	8.3	8.5
Min, max	5.8, 12.0	5.6, 15.5	5.4, 12.5
Abdominal pain, n (%)			
Absent	94 (71)	158 (61)	88 (68)
Mild	32 (24)	85 (33)	36 (28)
Moderate	7 (5)	16 (6)	5 (4)
Severe	0	1 (<1)	0
Anorexia, n (%)			
Absent	61 (46)	114 (44)	60 (47)
Mild	54 (41)	105 (40)	48 (37)
Moderate	18 (14)	36 (14)	16 (12)
Severe	0	5 (2)	5 (4)
Chills and rigors, n (%)			
Absent	8 (6)	18 (7)	8 (6)
Mild	47 (35)	88 (34)	35 (27)
Moderate	37 (28)	66 (25)	38 (29)
Severe	41 (31)	88 (34)	48 (37)
Coughing, n (%)			
Absent	109 (82)	221 (85)	103 (80)
Mild	22 (17)	39 (15)	22 (17)

Baseline risk Factor / Disease Characteristics	CQ alone (N=133)	CQ+TQ (N=260)	CQ+PQ (N=129)
Moderate	2 (2)	0	4 (3)
Diarrhea, n (%)			
Absent	127 (95)	241 (93)	120 (93)
Mild	4 (3)	17 (7)	7 (5)
Moderate	2 (2)	2 (<1)	1 (<1)
Severe	0	0	1 (<1)
Dizziness, n (%)			
Absent	50 (38)	92 (35)	47 (36)
Mild	60 (45)	125 (48)	61 (47)
Moderate	19 (14)	38 (15)	16 (12)
Severe	4 (3)	5 (2)	5 (4)
Headache, n (%)			
Absent	6 (5)	7 (3)	4 (3)
Mild	36 (27)	79 (30)	39 (30)
Moderate	29 (22)	74 (28)	37 (29)
Severe	62 (47)	100 (38)	48 (37)
Nausea, n (%)			
Absent	55 (41)	120 (46)	60 (47)
Mild	53 (40)	85 (33)	45 (35)
Moderate	24 (18)	51 (20)	24 (19)
Severe	1 (<1)	4 (2)	0
Pruritus/itching, n (%)			
Absent	118 (89)	214 (82)	111 (86)
Mild	12 (9)	29 (11)	11 (9)
Moderate	2 (2)	17 (7)	7 (5)
Severe	1 (<1)	0	0
Vomiting, n (%)			
Absent	93 (70)	190 (73)	93 (72)
Mild	32 (24)	51 (20)	28 (22)
Moderate	8 (6)	19 (7)	8 (6)
Splenomegaly, n (%)			
Yes	4 (3)	13 (5)	4 (3)
No	129 (97)	247 (95)	125 (97)
Previous malarial episode, n (%)			
Yes	106 (80)	219 (84)	109 (84)
No	26 (20)	41 (16)	18 (14)
Unknown	1 (<1)	0	2 (2)
***P. vivax* - asexual parasite count/µL**			
Median	5615.0	5313.5	4380.0
Minimum	101	112	125
Maximum	66010	99604	87380
***P. vivax* - gametocyte parasite count/µL**			
Median	55.0	53.5	31.0
Minimum	0	0	0
Maximum	1110	7201	4949

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

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

Table 29: TAF112582 Part 2: Treatment compliance (micro-ITT population)

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

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

Source: Table 15, Study Report

Recurrence-Free Efficacy

The estimated recurrence-free efficacy proportions over 6 months from the Kaplan-Meier analysis were 62.4% and 27.7% in the CQ+TQ and CQ alone group, respectively. Time to event analysis indicated that CQ+TQ treatment statistically significantly reduced the risk of recurrence by 70.1% (95% CI [59.6%, 77.8%], derived from HR=0.299, 95% CI [0.222, 0.404], p<0.001), compared with the CQ alone group. The risk of recurrence was also significantly reduced in the CQ+PQ group compared with the CQ alone group. The proportions of subjects who were censored in the primary analysis were similar across the three groups (Table 30). Our analysis results matched the Applicant's analysis results. We also conducted a sensitivity analysis by assuming early censoring=failure (see table). The conclusions were similar, although the treatment effect was slightly reduced. Additionally, an analysis assuming early censoring=success in the CQ alone and early censoring=failure for the CQ+TQ group (a worst-case scenario) continued to show statistical significance of CQ+TQ over CQ alone (not reported). This extreme method of handling censoring resulted in statistically significant results, indicating that missing data is not impacting our ability to make conclusions from this trial.

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

Table 30. TAF112582 Part 2: Recurrence-free efficacy over 6 months (micro-ITT population)

	CQ alone (N=133)	CQ+TQ (N=260)	CQ+PQ (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)
No demonstration of initial clearance of P. vivax parasitemia	1 (<1)	2 (<1)	0
Taking drug with anti-malarial action in first 6 months (and not parasitemic)	5 (4%)	11 (4%)	4 (3%)
No parasite-free confirmation at 6 month assessment	4 (3%)	7 (3%)	6 (5%)
Recurrence-free efficacy rate at 6 months[a]			
Estimate (95% CI)	27.7 (19.6,36.3)	62.4 (54.9,69.0)	69.6 (60.2,77.1)
Hazard ratio of risk of recurrence vs CQ alone[b]			
Estimate (95% CI)		0.299 (0.222,0.404)	0.262 (0.178,0.387)
p-value		<0.001	<0.001
Hazard ratio of risk of recurrence vs CQ alone[b] (Censoring=failure)			
Estimate (95% CI)		0.346 (0.262, 0.456)	0.312 (0.219, 0.443)
p-value		<0.001	<0.001
Odds ratio of risk of recurrence vs CQ alone[b] (missing=failure)			
Estimate (95% CI)		0.241 (0.152,0.382)	0.198 (0.117,0.335)
p-value		<0.001	<0.001

[a] Kaplan-Meier methodology

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

Early Treatment Failure and Recrudescence by Day 32

Early failures were defined as subjects who did not demonstrate initial clearance of *P. vivax* parasitemia OR demonstrated initial clearance and had a subsequent non-zero asexual *P. vivax* parasite count on or before Day 32. Only 3 subjects in the CQ+TQ (1.2%) and 2 subjects in the CQ alone group (1.5%) experienced early treatment failures. Three of these 5 subjects (1 CQ

alone and 2 CQ+TQ) withdrew from the study prior to Day 5 and are not available for assessment of initial clearance of parasitemia. These three subjects were censored for not demonstrating initial clearance of *P. vivax* parasitemia in the Applicant's analysis. For the remaining 2 subjects, one subject, who was in the CQ alone group (0.8%), experienced recrudescence prior to Day 33 and the other subject in the TQ+CQ group experienced treatment failure. These two subjects were considered as heterologous of parasitemia in 6 months after initial clearance in the Applicant's analysis.

Table 31. TAF112582 Part 2: Early treatment failure by Day 32 (micro-ITT Population)

	CQ alone (N=133) n (%)	CQ+TQ (N=260) n (%)	CQ+PQ (N=129) n (%)
Number of subjects with early failure	2 (1.5)	3 (1.2)	0
Subjects failing to demonstrate initial clearance	1	2	0
Subjects demonstrating initial clearance but experienced failure	1	1	0

Source: Table 7.28, Study Report

Incidence of *P. falciparum* Malaria

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

Early Response to Treatment

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

Table 32. TAF112582 Part 2: Analysis of early response to treatment (micro-ITT population)

	CQ alone (N=133)	CQ+TQ (N=260)	CQ+PQ (N=129)
Number of subjects, n (%)			
Parasite clearance achieved	129 (97)	254 (98)	127 (98)
Censored, parasite clearance not achieved	4 (3)	6 (2)	2 (2)
Time to parasite clearance (hours)*			
Median (95% CI)	43 (41,48)	45 (42,47)	42 (39,45)
Number of subjects, n (%)			
Fever clearance achieved	48 (36)	102 (39)	47 (36)
Censored, at Baseline	85 (64)	158 (61)	82 (64)
Time to fever clearance (hours)			
Median (95% CI)	7 (5,14)	7 (5,12)	8 (6,18)
Number of subjects, n (%)			

	CQ alone (N=133)	CQ+TQ (N=260)	CQ+PQ (N=129)
Gametocyte clearance achieved	85 (64)	168 (65)	79 (61)
Censored, at Baseline	47 (35)	92 (35)	49 (38)
Censored, gametocyte clearance not achieved	1 (<1)	0 (0)	1 (<1)
Time to gametocyte clearance (hours)			
Median (95% CI)	38 (32,40)	39 (37,41)	36 (24,41)

*Source: Table 20, Study Report. We reproduced the time to parasite clearance median and 95% CI closely.

Subgroup Analyses by Gender, Race, Age, Body Weight, Country, Baseline Parasite Count and CYP2PD Classification

Recurrence-free efficacy at 6 months by gender, race, age, body weight, body mass index, geographic location (country), baseline parasite count, and CYP2PD classification is presented in the following table. No concerning signals were seen in these analyses.

Table 33. TAF112582 Part 2: Recurrence-free efficacy at 6 month by gender, race, age, and body weight, body mass index, country, and baseline parasite count (micro-ITT population)

n/N (%)	CQ alone (N=133)	CQ+TQ (N=260)	CQ+PQ (N=129)
Gender			
Male	23/97 (24)	108/196 (55)	67/99 (65)
Female	12/36 (33)	47/64 (73)	19/30 (63)
Race			
American Indian or Alaska native	13/43 (30)	53/81 (65)	24/41 (59)
Asian - Southeast Asian heritage	8/26 (31)	28/50 (56)	21/26 (81)
Black or African American	3/14 (21)	16/28 (57)	10/13 (77)
Multiple	11/47 (23)	56/97 (58)	28/47 (60)
White	0/3 (0)	2/4 (50)	0/2 (0)
Age in years			
<65	34/131 (26)	150/253 (59)	81/126 (64)
≥65	1/2 (50)	5/7 (71)	2/3 (67)
Body weight (kg)			
<60	11/46 (24)	75/115 (65)	38/54 (70)
≥60	24/87 (28)	80/145 (55)	45/75 (60)
Body Mass Index (kg/m^2)			
<30	14/78 (18.0)	86/145 (59.3)	48/72 (66.7)
≥30	21/55 (38.2)	69/115 (60.0)	35/57 (61.4)
Country			
Brazil	12/53 (23)	61/105 (58)	30/52 (58)
Ethiopia	3/14 (21)	16/28 (57)	10/13 (77)
Cambodia	1/10 (10)	6/19 (32)	6/9 (67)
Peru	12/40 (30)	50/77 (65)	22/38 (58)
Philippines	0/1 (0)	3/3 (100)	2/2 (100)
Thailand	7/15 (47)	19/28 (68)	13/15 (87)
Baseline parasite count (/µL)			
< 5000	18/63 (29)	77/128 (60)	43/67 (64)
≥ 5000	17/70 (24)	78/132 (59)	40/62 (65)
CYP2D6 classification			

n/N (%)	CQ alone (N=133)	CQ+TQ (N=260)	CQ+PQ (N=129)
Extensive metabolizer	18/94 (19.1)	112/192 (58.3)	58/87 (66.7)
Intermediate metabolizer	15/34 (44.1)	33/54 (61.1)	22/35 (62.9)
Poor metabolizer	0/2 (0)	2/3 (66.7)	0/3 (0)

Conclusions

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

7.2.3.Study TAF116564

Trial Objectives

The primary objective was to investigate the occurrence of clinically relevant hemolysis in adult subjects with *P. vivax*. The incidence of hemolysis in the subgroup of female patients with moderate (40% to 70%) G6PD activity was of particular interest.

One of the secondary endpoints was to compare the clinical and parasitological efficacy, safety and tolerability of TQ to PQ as a radical cure for adult subjects with *P. vivax* malaria when co-administered with CQ.

Trial Design and Endpoints

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

The duration of the study was 180 days, including screening and randomization to treatment (Day 1), 3 in-hospital days (Days 1 to 3), 4 outpatient visits while on treatment with study medication (Days 5, 8, 11 and 15) and 7 follow-up visits (Days 22, 29, 60, 90, 120, 150 and 180). Subjects must have had a blood smear that was positive for *P. vivax* at entry. Blood smears were taken for parasitological assessment twice a day for the first 3 days of the study, or until 2 consecutive thick blood smears were negative for *P. vivax*.

The primary endpoints for this study were safety endpoints. Efficacy endpoints were secondary, which included:

- Recurrence-free efficacy 6 months post-dosing
- Recurrence-free efficacy four months post-dosing
- Time to recurrence
- Parasite clearance time
- Fever clearance time

- Gametocyte clearance time
- Recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 32 (ie, blood stage treatment failure).
- Incidence of genetically homologous and genetically heterologous *P. vivax* infections (determined by PCR)
- Incidence of *P. falciparum* malaria

Among these efficacy endpoints, no primary endpoint was defined. The reviewer will focus on the recurrence-free efficacy 6 months post-dosing. For relapse-free efficacy and time to relapse, the following definitions were used.

A subject would be considered to have demonstrated relapse-free efficacy at 6 months for the purposes of the analysis if all of the following are true:

- Subject had a non-zero P. vivax asexual parasite count at baseline. Subjects with no asexual *P. vivax* parasites at this time point would be censored with time to relapse = 0 days.
- Subject demonstrated initial clearance of *P. vivax* parasitemia. This was defined as two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval. Subjects who did not meet this criterion would be classified as relapses, with time to relapse = 0 days.
- Subject had no positive asexual *P. vivax* parasite count at any assessment prior to or on Study Day 201 following initial parasite clearance. Subjects who had a positive count would be classified as relapses, with time to relapse = (date of first positive count) – (date of Study Day 1) days.
- Subject did not take a concomitant medication with anti-malarial activity at any point between Study Day 1 and their last parasite assessment. Subjects who did take a drug with anti-malarial activity but never had a positive asexual *P. vivax* parasite count after initial clearance would be censored, with time to relapse censored at (date of last negative parasite assessment prior to concomitant medication start) – (date of Study Day 1). If a subject had not had a negative assessment prior to the concomitant medication start date, they would be censored at 0.
- Subject was parasite-free at 6 months. This was defined as a negative asexual *P. vivax* parasite count at the first parasite assessment performed on or after Study Day 166.

Subjects who did not have a positive asexual *P. vivax* parasite count following initial clearance but where the final parasite count occurred before Study Day 166 was considered to be censored, with time to relapse censored at (Date of final parasite assessment) – (date of Study Day 1).

If a subject had a relapse outcome and a censored outcome, the subject was considered to be a relapse, even if the time point of the relapse was later than the time point of censoring. For example, a subject who took a medication with anti-malarial activity at Study Day 32, but relapsed on Study Day 68 will be treated as a relapse at Study Day 68.

Key Inclusion and Exclusion Criteria

Inclusion criteria

Inclusion criteria included, but were not limited to:

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

Exclusion criteria

Exclusion criteria included, but were not limited to:

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

Statistical Analysis Plan

Analysis Populations

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

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

Analysis Methods

The primary comparisons of interest between the 2 treatment arms were the proportion of all subjects with *P. vivax* experiencing clinically relevant hemolysis, and the proportions in the subgroup of females with *P. vivax* and moderate G6PD deficiency. For results of these analyses, please see Section 10 of the review.

Other comparisons included clinical and parasitological efficacy, safety and tolerability of TQ +CQ compared to CQ+PQ. Estimates for the recurrence-free efficacy rate at 6 and 4 months and time to recurrence were determined for each treatment group using the Kaplan-Meier method.

A Cox proportional hazards model with region and treatment as covariates was used. Subjects who did not have a positive *P. vivax* asexual count at baseline, clear the original infection, took a concomitant medication with anti-malarial activity, or could not be confirmed parasite-free at 6 or 4 months were censored.

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

For all analyses of the micro-ITT population, subjects with missing values will not be excluded from any statistical analysis.

This study was not designed to assess noninferiority of TQ to PQ as this study was primarily a safety study and there were no hypotheses tested. We conducted a meta-analysis (random effect model) using the data from TAF112582 Part 1 and Part 2 which showed that the treatment effect of CQ+PQ compared to CQ alone (CQ+PQ minus CQ) was 35.2%, with a 95% CI [26.1%, 45.2%]. Therefore, a noninferiority margin of less than 26% could be used to help interpret the results of the study.

Protocol Amendments

Five protocol amendments were made, with no changes which would affect efficacy analyses.

Compliance with Good Clinical Practices

This study was performed in compliance with Good Clinical Practices.

Financial Disclosure

There were no financial interests to disclose.

Patient Disposition

The study was conducted between 4/28/2015 and 11/4/2016 in 7 sites of 5 countries (Brazil, Colombia, Peru, Thailand, and Vietnam).

A total of 251 subjects out of 369 screened for eligibility were randomized. The majority of the randomized subjects (97%) completed the study. Only 4% of subjects stopped treatment prematurely in both groups. All randomized subjects were included in the micro-ITT population and safety population. About 88% of the subjects in the micro-ITT population were included in the PP population.

Table 34. TAF116564: Patient disposition

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

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

Protocol Violations/Deviations

Protocol violations and deviations are presented in the following table. The proportions of

subjects with these violations and deviations were low and comparable between the treatment groups.

Table 35. TAF116564: Protocol violations and deviations (micro-ITT population)

	CQ+TQ (N=166) n (%)	CQ+PQ (N=85) n (%)
Assessments and/or procedures	27 (16)	13 (15)
Failure to comply with dosing procedure	10 (6)	5 (6)
Failure to report SAE, pregnancy, or liver function abnormalities per-protocol	2 (1)	0
Informed consent process	5 (3)	7 (8)
Missed assessment or procedure	10 (6)	5 (6)
Other	4 (2)	3 (4)
Eligibility criteria not met	3 (2)	0
Other protocol deviation category	2 (1)	1 (1)
Prohibited medication or device	6 (4)	2 (2)
Visit, assessment or timepoint window	19 (11)	7 (8)
Other	1 (<1)	1 (1)
Out of window - efficacy assessment	15 (9)	5 (6)
Out of window - PK collection	6 (4)	0
Out of window - safety assessment	3 (2)	1 (1)

Demographic Characteristics

Demographic characteristics (age, sex, race, geographic location, and body mass index) are presented in the following table. The two groups were comparable with respect to these characteristics. The mean age was 38 years old. The majority of the subjects were male. The three races of American Indian or Alaska Native, Asian, and Multiple accounted for 99% of the subjects. Most subjects were from Brazil and Peru.

Table 36. TAF116564: Demographic characteristics

	CQ+TQ (N=166)	CQ+PQ (N=85)
Age in years		
Mean(SD)	37.5 (14.28)	37.7 (14.69)
Range	16, 75	15, 74
Sex, n(%)		
Male	114 (69)	53 (62)
Female	52 (31)	32 (38)
Race, n(%)		
American Indian or Alaska Native*	87 (52)	43 (51)
Asian (Southeast Asian Heritage)	41 (25)	23 (27)
Black or African American	2 (1)	0
Multiple†	36 (22)	19 (22)
Body mass index (kg/m2)		
Mean	25.6	25.5
Median	24.79	25.24
Min, Max	(16.7, 48.9)	(17.4, 40.4)

	CQ+TQ (N=166)	CQ+PQ (N=85)
Country, n(%)		
Brazil	45 (27.1)	23 (27.1)
Colombia	13 (7.8)	6 (7.1)
Peru	67 (40.4)	33 (38.8)
Thailand	12 (7.2)	8 (9.4)
Vietnam	29 (17.5)	15 (17.7)

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

Other Baseline Characteristics

The following table presents a summary of malaria signs and symptoms at baseline. The two groups had similar profiles for these baseline characteristics.

Table 37. TAF116564: Summary of malaria signs and symptoms (safety population)

	CQ+TQ (N=166) n(%)	CQ+PQ (N=85) n(%)
Abdominal pain, n (%)		
Absent	117 (70)	68 (80)
Mild	40 (24)	12 (14)
Moderate	9 (5)	5 (6)
Anorexia, n (%)		
Absent	80 (48)	49 (58)
Mild	46 (28)	15 (18)
Moderate	36 (22)	19 (22)
Chills and rigors, n (%)		
Absent	9 (5)	5 (6)
Mild	32 (19)	22 (26)
Moderate	62 (37)	23 (27)
Severe	63 (38)	35 (41)
Coughing, n (%)		
Absent	141 (85)	65 (76)
Mild	20 (12)	19 (22)
Moderate	5 (3)	1 (1)
Diarrhea, n (%)		
Absent	140 (84)	73 (86)
Mild	24 (14)	11 (13)
Moderate	2 (1)	0
Severe	0	1 (1)
Dizziness, n (%)		
Absent	72 (43)	36 (42)
Mild	64 (39)	27 (32)
Moderate	28 (17)	21 (25)
Severe	2 (1)	1 (1)
Headache, n (%)		
Absent	7 (4)	5 (6)
Mild	23 (14)	13 (15)
Moderate	59 (36)	28 (33)
Severe	77 (46)	39 (46)

	CQ+TQ (N=166) n(%)	CQ+PQ (N=85) n(%)
Nausea, n (%)		
Absent	80 (48)	49 (58)
Mild	46 (28)	15 (18)
Moderate	36 (22)	19 (22)
Severe	4 (2)	2 (2)
Pruritus/itching, n (%)		
Absent	151 (91)	76 (89)
Mild	7 (4)	6 (7)
Moderate	8 (5)	3 (4)
Vomiting, n (%)		
Absent	117 (70)	71 (84)
Mild	38 (23)	11 (13)
Moderate	11 (7)	3 (4)

The following table shows a summary of splenomegaly, previous malarial episodes, and *P. vivax* parasite counts at baseline. The two groups had similar distributions with these baseline characteristics.

Table 38. TAF116564: Splenomegaly, previous malarial episodes, and *P. vivax* parasite counts at baseline (micro-ITT population)

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

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

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

Table 39. TAF116564: Exposure and treatment compliance (micro-ITT population)

	CQ+TQ (N=166) n/N (%)	CQ+PQ (N=85) n/N (%)
Number of compliant doses of CQ		
2	1 (<1)	1 (1)
3	165 (>99)	84 (99)
Was subject compliant with TQ?		

	CQ+TQ (N=166) n/N (%)	CQ+PQ (N=85) n/N (%)
Yes	165 (>99)	84 (99)
No	1 (<1)	1 (1)
Total number of PQ doses taken		
<12	6 (4)	1 (1)
at least 12	160 (96)	83 (98)
Missing	0	1 (1)

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

Efficacy Results

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

Table 40. TAF116564: Recurrence-free efficacy over 6 months (micro-ITT population)

	CQ+TQ (N=166)	CQ+PQ (N=85)
Number of subjects, n(%)		
Subjects observed to recurrence prior to or at 6 months	42 (25)	20 (24)
Censored, prior to 6-month assessment	12 (7)	5 (6)
Taking drug with anti-malarial action in first 6 months (and were not parasitemic)	6 (4)	2 (2)
No confirmation of parasite-free at 6 month assessment	6 (4)	3 (4)
Recurrence-free at 6 months	112 (67)	60 (71)
Recurrence-free efficacy rate at 6 months, %		
Estimate (95% CI)	72.7 (64.8,79.2)	75.1 (64.2,83.2)
Hazard ratio of risk of recurrence vs CQ+PQ		
Estimate (95% CI)	0.984 (0.577,1.678)	1

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

Table 41. TAF116564: Analysis of recurrence-free efficacy at 6 months (logistic regression, missing=failure, micro-ITT population)

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

				Comparison with CQ+PQ	
Treatment	**N**	**Subjects Recurrence-Free (%)**	**Subjects with a Recurrence (%)**	**Odds Ratio of Recurrence**	**95% CI**
CQ+PQ	85	60 (71)	25 (29)		

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

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

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

Gender, Race, Age, Weight, Body Mass Index, Country, and Baseline Parasite Count

The subgroup analysis results are presented in the following table. Results were generally consistent with the overall results. Note that some sample sizes were too small to make any conclusions. As would be expected, there were some subgroups that favor CQ+PQ while others favor CQ+TQ. It is difficult however to conclude this was due to anything other than random variation.

Table 42. TAF116564: Analysis of recurrence-free efficacy at 6 months by gender, race, age, weight, body mass index, country, baseline parasite count (micro-ITT population)

	CQ+TQ (N=166)	CQ+PQ (N=85)
Sex, n(%)		
Male	78/114 (68.4)	38/53 (71.7)
Female	34/52 (65.4)	22/32 (68.8)
Age (yrs)		
<65	108/159 (67.9)	59/84 (70.2)
≥65	4/7 (57.1)	1/1 (100.0)
Race, n (%)		
American Indian or Alaska Native	55/87 (63.2)	27/43 (62.8)
Asian	30/41 (73.2)	21/23 (91.3)
Black or African American	1/2 (50.0)	0
Multiple	26/36 (72.2)	12/19 (63.2)
Country, n (%)		
Brazil	31/45 (68.9)	15/23 (65.2)

	CQ+TQ (N=166)	CQ+PQ (N=85)
Colombia	8/13 (61.5)	4/6 (66.7)
Peru	43/67 (64.2)	20/33 (60.6)
Thailand	9/12 (75.0)	8/8 (100.0)
Vietnam	21/29 (72.4)	13/15 (86.7)
Weight (kg)		
<60	43/63 (68.3)	25/31 (80.7)
≥60	69/103 (67.0)	35/54 (64.8)
Body Mass Index (kg/m^2)		
<30	99/138(71.7)	53/72(73.6)
≥30	13/28(46.4)	7/13(53.9)
Baseline parasite count (/µL)		
<5000	63/100 (63.0)	31/42 (73.8)
≥5000	49/66 (74.2)	29/43 (67.4)

Conclusions
Study TAF116564 provides supportive evidence of efficacy. Though the primary objective of this study was safety, the recurrence-free efficacy endpoint could have met a conservative 22% noninferiority margin, which is smaller than the conservative treatment effect of CQ+PQ compared to CQ alone as estimated from the previous studies (26%).

7.3.Integrated Review of Effectiveness

See Section 7.4.3

7.4.Summary and Conclusions

7.4.1.Summary and Conclusions – Statistics

The efficacy of TQ in addition to CQ was evaluated in three clinical trials. All three trials were randomized, double-blinded, double-dummy, controlled trials. CQ was used to clear the initial blood stage infection in all three trials. Two of the trials included a placebo group of CQ alone. These trials demonstrated a statistically significant treatment effect for the proposed indication of the radical cure (prevention of relapse) of *P. vivax*. One trial used CQ+PQ as the control group and this trial demonstrated that the two treatment groups produced similar efficacy results, supporting the efficacy of TQ.

7.4.2.Summary and Conclusions - Clinical

Results from the three clinical trials demonstrated that TQ 300mg single-dose co-administered with CQ x 3 days is an effective treatment for the radical cure of *P. vivax* malaria. In the phase 3 placebo-controlled efficacy trial, study TAF112582- part 2, the estimated recurrence-free efficacy proportions over 6 months in the Kaplan-Meier analysis were 62.4% and 27.7% in the CQ+TQ and CQ alone group, respectively. Time to event analysis indicated that CQ+TQ treatment statistically significantly reduced the risk of recurrence by 70.1% (95% CI [59.6%, 77.8%], derived from HR=0.299, 95% CI [0.222, 0.404], p<0.001), compared with the CQ alone

group. The risk of recurrence was also significantly reduced in the CQ+PQ group compared with the CQ alone group. Recurrence free efficacy results in the other two trials were supportive of the efficacy of the TQ 300 mg + CQ regimen. In the phase 2b dose escalation trial, among the four CQ+TQ groups, the TQ 300 mg group achieved the highest relapse-free efficacy versus CQ control, i.e. 84% vs. 39% at 6 months. Recurrence-free efficacy for TQ+CQ was consistent across geographic regions in the placebo-controlled trials and demonstrated improvement over CQ. Relapse cannot be reliably distinguished from reinfection in these trials; therefore, the estimates of recurrence-free efficacy at 6 months are probably conservative.

The standard of care for the radical cure (prevention of relapse) of *P. vivax* malaria includes a schizontocidal antimalarial, usually CQ x 3 days, co-administered with a 14-day course of PQ. Adherence to CQ and PQ is vital in achieving full effectiveness of the *P. vivax* malaria treatment, including the prevention of relapse of *P. vivax* infection in an individual patient and in global malaria elimination efforts. Eliminating *P. vivax* hypnozoites decreases morbidity associated with malaria relapse in a patient and reduces transmission potential to other individuals. Improved patient education along with the availability of a rapid and accurate test for G6PD status at the point of care are crucial to this endeavor.

The Applicant provided evidence from published literature that nonadherence of PQ is related to treatment failures in *P. vivax* malaria. Several publications report that patients are less likely to take PQ once their symptoms have abated and adherence to the full 14-day course is often low. TQ as a single-dose for radical cure of *P. vivax* would be a major improvement in compliance over the 7- to 14-day course of PQ. An improvement in compliance with single-dose TQ could improve clinical outcomes by reducing morbidity associated with subsequent relapse of *P. vivax* malaria. If TQ were used widely for radical cure, it could potentially help reduce the global burden of *P. vivax* malaria.

PQ has complicated metabolic pathways and some pathways are thought to be mediated by CYP2D6 which contributes to the conversion to the active metabolite. Patients who are poor or intermediate 2D6 metabolizer may have suboptimal exposure to the active metabolite and in turn, may have poor response to PQ treatment; however, this does not appear to have been confirmed in a clinical trial. The number of poor/intermediate 2D6 metabolizer in the phase 3 clinical trials were too small to make a conclusion about TQ efficacy in this subgroup. In current clinical practice, it is not always feasible to test individuals for the 2D6 metabolizer status prior to dosing with PQ. However, there is no evidence that CYP2D6 polymorphism may impact TQ efficacy and a potential efficacy advantage of TQ over PQ in this subpopulation needs further evaluation.

7.4.3.Assessment of Efficacy Across Trials

Due to the lack of a CQ alone arm in Study TAF116564 and the different randomization ratios used in TAF115582 Part 1 and the other two studies, we did not pool the three studies. This section contains study results side-by-side for ease of comparison.

The primary efficacy endpoint considered in this review was recurrence-free efficacy 6 months post-dosing (also referred to as relapse-free efficacy). The results of TQ 300 mg single dose given with CQ for three days are given below for the three clinical trials along with the control group used for each trial.

Table 43. Analysis of recurrence-free efficacy at 6 months by study

	TAF112582 Pt 1		TAF112582 Pt 2		TAF116564	
	CQ alone (N=54)	CQ+TQ (N=57)	CQ alone (N=133)	CQ+TQ (N=260)	CQ+TQ (N=166)	CQ+PQ (N=85)
Number of subjects, n(%)						
Recurrence-free at 6 months	21 (39)	48 (84)	35 (26)	155 (60)	112 (67)	60 (71)
Recurrence prior to or at 6 months	31 (57)	6 (11)	88 (66)	85 (33)	42 (25)	20 (24)
Censored, prior to 6 month assessment	2 (4)	3 (5)	10 (8)	20 (8)	12 (7)	5 (6)
Recurrence-free efficacy rate at 6 months						
Estimate (95% CI)	37.5 (23, 52)	89.2 (77, 95)	27.7 (20, 36)	62.4 (55, 69)	72.7 (65, 79)	75.1 (64, 83)

Subpopulations

The subgroup analyses for these trials were conducted by gender, race, age, country, parasite count, and CYP2D6 metabolizer classification (only in TAF112582 Part 2). The following table shows the subgroup analysis results for the 300 mg TQ group and control groups only. In general, the results were consistent with the overall results. However, the sample sizes in some subgroups were too small to make reliable conclusions. In addition, there were no subjects from the United States and only 2.4% of the subjects were 65 years or older.

Table 44. Subjects with relapse-free efficacy at 6 months (primary analysis) by demographic characteristic

	TAF112582 Part 1		TAF112582 Part 2		TAF116564	
	CQ alone (N=54)	TQ+CQ (N=57)	CQ alone (N=133)	CQ+TQ (N=260)	CQ+TQ (N=166)	CQ+PQ (N=85)
Gender						
Male	17/39 (44)	37/43 (86)	23/97 (24)	108/196 (55)	78/114 (68)	38/53 (72)
Female	4/15 (27)	11/14 (79)	12/36 (33)	47/64 (73)	34/52 (65)	22/32 (69)
Race						
American Indian	4/27 (15)	21/29 (72)	13/43 (30)	53/81 (65)	55/87(63)	27/43(63)
Asian	17/26 (65)	27/28 (96)	8/26 (31)	28/50 (56)	30/41 (73)	21/23 (91)
Black			3/14 (21)	16/28 (57)	1/2 (50.0)	0
Multiple	0/1		11/47 (23)	56/97 (58)	26/36 (72)	12/19 (63)
White			0/3 (0)	2/4 (50)		
Age in years						
<65	20/53 (38)	48/57(84)	34/131 (26)	150/253 (59)	108/159(68)	59/84 (70)
≥65	1/1 (100)		1/2 (50)	5/7 (71)	4/7 (57)	1/1 (100)
Country						
Brazil	1/6(17)	5/6(83)	12/53 (23)	61/105 (58)	31/45 (69)	15/23 (65)

	TAF112582 Part 1		TAF112582 Part 2		TAF116564	
	CQ alone (N=54)	TQ+CQ (N=57)	CQ alone (N=133)	CQ+TQ (N=260)	CQ+TQ (N=166)	CQ+PQ (N=85)
India	9/10(90)	9/9(100)				
Ethiopia			3/14 (21)	16/28 (57)		
Cambodia			1/10 (10)	6/19 (32)		
Columbia					8/13 (62)	4/6 (67)
Peru	3/22(14)	16/23 (70)	12/40 (30)	50/77 (65)	43/67 (64)	20/33 (61)
Philippines			0/1 (0)	3/3 (100)		
Thailand	8/16 (50)	18/19 (95)	7/15 (47)	19/28 (68)	9/12 (75)	8/8 (100)
Vietnam					21/29 (72)	13/15 (87)

Table 45. Subjects with relapse-free efficacy at 6 months (primary analysis) by baseline characteristics

	TAF112582 Part 1		TAF112582 Part 2		TAF116564	
	CQ alone (N=54)	CQ+TQ (N=57)	CQ alone (N=133)	CQ+TQ (N=260)	CQ+TQ (N=166)	CQ+PQ (N=85)
Weight (kg)						
<60	14/30 (47)	26/30 (87)	11/46 (24)	75/115 (65)	43/63 (68)	25/31 (81)
≥60	7/24 (29)	22/27 (82)	24/87 (28)	80/145 (55)	69/103 (67)	35/54 (65)
Body Mass Index (kg/m^2)						
<30	19/50 (38)	46/54 (85)	14/78 (18)	86/145 (59)	99/138 (72)	53/72 (74)
≥30	2/4 (50)	2/3 (67)	21/55 (38)	69/115 (60)	13/28 (46)	7/13 (54)
Baseline parasite count (/µL)						
≤7500	14/37(38)	32/39(82)				
>7500	7/17(41)	16/18(89)				
<5000			18/63 (29)	77/128 (60)	63/100 (63)	31/42 (74)
≥5000			17/70 (24)	78/132 (59)	49/66 (74)	29/43 (67)
CYP2D6 metabolizer classification						
Extensive			18/94 (19)	112/192 (58)		
Intermediate			15/34 (44)	33/54 (61)		
Poor			0/2 (0)	2/3 (67)		

8 Clinical Microbiology Review

8.1. Nonclinical Microbiology

8.1.1. Mechanism of Action

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

8.1.1.1. Effect on hematin polymerization

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

8.1.1.2. Effect on mitochondrial function

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

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

8.1.1.3. Effect on erythrocytes

Bhuyan et al. (2016) reported shrinkage of the human erythrocytes as well as phospholipid scrambling of the erythrocyte cell membrane after incubation with TQ (500 ng/mL) for 48 hours. This was associated with stimulation of Ca^{2+} entry, oxidative stress and possibly activation of casein kinase. Such a TQ induced eryptosis is similar to apoptosis of the parasites.

TQ induced eryptosis may be beneficial in sequestering the intracellular parasites. PQ or CQ were not tested.

8.1.2. Activity in vitro

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

8.1.2.1. Activity against asexual parasites

Russell et al., 2003 reported the activity of TQ against 34 clinical isolates of *P. vivax* from patients, in Thailand, successfully treated with CQ. Testing was performed by a modified World Health Organization microtest for determination of *P. falciparum* drug sensitivity. Briefly, 1,000 to 50,000 ring stage parasites/µL were resuspended to a hematocrit of 40% in AB^+ human serum; 50 µL of blood serum mixture (4% hematocrit) was incubated with different concentrations of TQ or other drugs including CQ until ≥50% of the ring stage parasites had matured to schizonts (~24 to 36 hours). The number of schizonts per 200 asexual stage parasites were counted on stained smears. The TQ mean IC_{50} and IC_{99} (99% inhibitory concentration) values were 9.74 and 14 µg/mL, respectively. The TQ IC_{99} value was about 88-fold higher than CQ. PQ was not tested.

8.1.2.2. Activity against gametocytes

Ponsa et al. (2003) reported the activity of TQ against the gametocytes of *P. vivax*. The activity was determined by assessing oocyst and sporozoite development within the mosquitoes. Briefly, mosquitoes (*Anopheles dirus*) were fed for 30 minutes on 1 mL of blood, collected from patients, living in Western Thailand and had gametocytes in the blood. All unengorged mosquitoes were removed. On Days 4, 8, 11, and 16 post-infection, mosquitoes were fed on uninfected mice that were administered different doses of TQ or other drugs, 90 minutes prior to feeding of mosquitoes. All engorged mosquitoes were followed, by phase contrast microscopy, for the presence of oocysts in the midgut and sporozoites in the salivary gland on Days 10 and 21, respectively. The results show that TQ was most effective in decreasing the development of oocysts and sporozoites in the mosquitoes treated on Day 4. PQ was ineffective in inhibiting sporozoite development.

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

8.1.2.3. Activity against exo-erythrocytic parasites

No studies were conducted to evaluate the activity of TQ against the exo-erythrocytic (liver) stages of the *Plasmodium* parasites.

8.1.3.Activity in vivo (Animal Studies)

The activity of TQ was reported in nonhuman primates infected with the parasitized erythrocytes of *P. vivax* or sporozoites and/or erythrocytes of *Plasmodium cynomolgi*. *P. cynomolgi* shares some of the phenotypic and biological characteristics with *P. vivax*. For example, relapse caused by dormant hypnozoites can occur following sporozoite challenge.

8.1.3.1. P. vivax and P. cynomolgi – monkeys infected with erythrocytic parasites

Several studies have reported the activity of TQ against erythrocytic parasites of *P. vivax* and *P. cynomolgi* in nonhuman primates, that include Panamanian monkeys, Rhesus monkeys and splenectomized monkeys. Animals were infected with parasitized erythrocytes. TQ was shown to be effective in clearing or reducing parasitemia; the activity varied with the experimental design and the doses tested. Recrudescence occurred that appears to be dose-dependent (for details see Appendix-15.5.1).

8.1.3.2. P. cynomolgi – monkeys infected with sporozoites

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

Causal prophylaxis: Treatment was initiated at different time intervals, prior to challenge with sporozoites, on the day of exposure, or 24 to 48 hours post-exposure. The results show that TQ is effective in preventing or delaying parasitemia. The activity of TQ varied with the experimental conditions including the TQ dose. Overall, the studies support the prophylactic activity of TQ (for details see Appendix-15.5.1).

Radical cure: Monkeys were treated with TQ after the development of parasitemia. The results show that TQ alone or in combination with CQ is effective in suppressing parasitemia and relapse. Anti-relapse activity is not dependent on CQ (for details see Appendix-15.5.1**Error! Reference source not found.**).

8.1.4. Drug Resistance

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

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

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

8.2. Clinical Microbiology

8.2.1. Parasitological assessments by blood smears

The parasitological evaluations in the three clinical trials include identification of *Plasmodium* species and quantitation of asexual and gametocyte forms using Giemsa stained thick and/or thin smears. Briefly, four slides (two thick films and one thin film, plus an additional unstained slide with both thick and thin films for contingency) were prepared at each time point. Appropriate quality control parameters were implemented that includes slide readings by at least 2 trained microscopists at the site laboratory. Also, the unstained contingency slide was shipped to the central laboratory, (b) (4) within a specified time, after preparation, for quality control. The results were expressed as positive or negative. If positive, the parasites were counted to determine parasite density and the results were expressed as asexual count/µL blood or gametocyte/µL blood (for details see Appendix-15.5.2). Time to clearance of asexual and gametocyte forms of the parasite was based on parasite numbers below the limit of detection in thick blood smear and remained undetectable at the second smear collected 6 to 12 hours later.

The results show that a single dose of TQ (300 mg) in combination with CQ is effective in reducing relapse rate. The radical cure (prevention of relapse) of *P. vivax* in subjects treated with TQ in combination with CQ was similar to that of PQ in combination with CQ. Asexual parasite clearance time, gametocyte clearance time, and fever clearance times were similar across treatment groups. Similar observations were made in different countries that include Africa, Southeast Asia and South America (For details see Section 7 above). Overall, the studies support TQ is effective against liver stages, asexual and gametocytes forms of *P. vivax*.

8.2.2. Genotyping by PCR and whole genome sequencing

Genotyping and whole genome sequencing was performed to distinguish relapse from recrudescence.

PCR: Blood samples were collected onto preprinted filter paper for DNA extraction and PCR analysis of the *P. vivax* genes MS16, Pv327, Pvmsp-1F3, PvCSP and PvAMA-1 at two time points, at Screening (Pre-dose) and at a follow-up visit when recrudescence/relapse/re-infection occurred. The objective of genotyping was to try to distinguish between recrudescence/relapse and reinfection. Testing was performed at the (b) (4). The details of the methods used, performance characteristics of the assay, as well as the quality control measures implemented were not included for review.

It is noted that insecticide-impregnated bed nets were provided to study participants to reduce the risk of re-infection.

Whole genome sequencing: Blood samples (4 mL) were collected for whole genome sequencing, of *P. vivax* parasites, at baseline and at the relapse visit. Extraction of the nucleic acid was performed at the sites and kept and shipped to (b) (4) for analysis.

Reviewer's comments:
The Applicant has not proposed to include corrected cure rates in the labeling. The performance characteristics and quality control measures for the genotyping methods used for determination of relapse vs. re-infection/new infection were not provided and therefore the results of the clinical specimens should be interpreted with caution. The uncorrected relapse rates as determined by slide examination are reported in Section 14 the labeling. This is appropriate.

8.2.3. Interpretive criteria

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

9 Review of Safety

9.1.1. Safety Review Approach

The clinical development program for TQ includes 33 clinical studies which are completed or ongoing. These studies include phase 1 single and multiple dose studies in healthy volunteers, human malaria challenge studies, drug-drug interaction studies, and phase 2 and 3 prophylaxis as well as therapeutic (radical cure) trials in patients with *P. vivax* malaria.

The objective of the safety review is to evaluate the safety of TQ 300 mg single-dose in patients with *P. vivax* malaria. This review focuses primarily on the safety of the TQ 300 mg single-dose proposed for the radical cure of *P. vivax* malaria from three randomized, double-blind, clinical trials, TAF112582 part 1 (phase 2b, dose-escalation), TAF112582 part 2 (phase 3, pivotal efficacy), and TAF116564 (phase 3, safety and efficacy), (see Table 46). The safety evaluation included analyses of the frequency and severity of adverse events and abnormal laboratory values for hematology and clinical chemistry parameters. Analyses of the safety data for TQ 300mg + CQ versus CQ (placebo equivalent) were conducted per trial and for the pooled TQ 300mg+CQ regimen across the two CQ only-controlled trials, TAF112582 part 1 &2. Analyses of safety of the pooled TQ 300mg + CQ regimen versus PQ + CQ treatment group were also conducted across the three trials TAF112582 part 1 &2 and TAF116564.

Safety data from two phase 1 placebo-controlled trials of TQ alone in healthy subjects are evaluated in this review, i.e., Study 201807, an ophthalmologic safety study of single-dose TQ and Study TAF114582, a Thorough QT (TQT) study. Safety data from a controlled healthy volunteer study, TAF110027, in G6PD deficient and G6PD normal subjects exposed to single-doses of TQ are also analyzed.

Recommendations from consultations with the Division of Transplant and Ophthalmology Products (DTOP), DPARP, and the QT-IRT team are summarized.

Adverse events of special interest such as hematologic, ophthalmic, and neuropsychiatric events known to be associated with quinoline antimalarial drugs are evaluated across TAF112582 part 1 &2 and TAF116564 and healthy volunteer studies. Clinical trial reports in the NDA are summarized in Table 46. See Section 6 for the clinical pharmacology reviewers' assessment of other phase 1 studies.

Note: This reviewer acknowledges Scott G. Runyan, B.S., Senior Analyst, JReview Support Team, for his contribution to many tables and graphs in this safety review.

Table 46. NDA 210-795: Clinical Trials

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 Interim	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 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

Source: NDA 210795, Applicant's Integrated Safety Summary (ISS).

9.1.2. Review of the Safety Database

Overall Exposure

Across the clinical development program, more than 4,000 subjects were exposed to TQ single- and multiple doses. The proposed regimen for clinical use, TQ 300mg single dose + CQ was evaluated in the placebo-controlled trials, TAF112582 parts 1 & 2, and in the safety trial TAF116564. In the phase 3 trials, CQ (600-mg free base on Days 1 and 2 with 300-mg free base on Day 3) was administered daily for 3 days and TQ 300 mg single-dose was administered on Day 1 or 2, i.e. TQ 300 mg + CQ. Subjects treated with PQ 15 mg once daily for 14 days also received CQ (Days 1 to 3), i.e., PQ+CQ. A total of 810 patients were exposed to TQ 300 mg single dose across the clinical program. A total of 483 patients with *P. vivax* malaria were exposed to TQ 300 mg + CQ in TAF112582 part 1 & 2 and TAF116564. TQ 300 mg was administered to 243 healthy subjects.
The datasets submitted in the NDA 210-795 are summarized in Table 47. Clinical datasets are located at \\Cdsesub1\evsprod\NDA210795\0000\m5\datasets.

Table 47. Exposure to TQ across the clinical development program

Dataset	Subjects	Total TQ Dose	N
All Studies	**All treated**	**Any**	**4129**
		<300 mg	392
		300 mg	810[a]
		>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**
		<300 mg	82
		300 mg	243
		>300 mg	395
Malaria Prophylaxis Studies	**All Treated**	**Any**	**2703**
		<300 mg	198
		300 mg	83
		>300 mg	2422

Source: Table 9.001, Table 9.002, Table 9.003, Table 9.004, Table 9.005, Table 9.006, Table 9.008
Note: Data from studies SB252263/003, SB252263/036, SB252263/050, SB252263/051, SB252263/052, SB252263/053 and SB252263/054 have been excluded from the pooled datasets. Five of these studies (SB252263/050, SB252263/051, SB252263/052, SB252263/053 and SB252263/054) were US Army-sponsored studies, and validated datasets containing the subject level data were not available to GSK. For Study SB252263/003, GSK were unable to locate validated datasets containing subject-level. Study SB252263/036 was terminated during dosing of the first subject because GSK voluntarily suspended TQ studies at the time due to safety findings in another study. The subject did not receive their complete randomized dose of TQ and was switched to receive PQ (m5.3.5.3, SDAP, Section 3).

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 SB252263/057 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 (m5.3.5.3, SDAP, Table 2).

Source: NDA 210795, Applicant's Clinical Overview, Table 15.

Clinical Trials Contributing Evidence of Safety

The design characteristics of the three key clinical trials contributing evidence for safety of the TQ 300 mg single-dose in patients with *P. vivax* malaria (confirmed by blood smear) are summarized in Table 48 and in section 7.2.

In these five clinical trials, 645 patients were exposed to TQ 300mg, (Table 48). TAF110027 (not shown) evaluated escalating doses of TQ including a TQ 300mg single-dose in G6PD-normal or G6PD-deficient but otherwise healthy subjects (n=51) and is included in the safety review.

Table 48. Clinical trials contributing evidence of safety for TQ 300 mg single-dose

	Primary Studies *P. vivax*		**Infected Patients**	**Specific Safety Studies**	
	TAF 112582 Part 1	**TAF 112582 Part 2**	**TAF 116564**	**201807 ophthalmic***	**TAF 114582, cardiac safety (QTcF)**
Study Design	Randomized double-blind	Randomized double-blind	Randomized, double-blind,	Randomized, single blind,	Randomized, single blind, placebo-

	Primary Studies *P. vivax*		Infected Patients	Specific Safety Studies	
	TAF 112582 Part 1	**TAF 112582 Part 2**	**TAF 116564**	**201807 ophthalmic***	**TAF 114582, cardiac safety (QTcF)**
	placebo, and active-controlled, double-dummy, parallel-group	placebo, and active-controlled, double-dummy, parallel-group	active-controlled, double dummy, parallel group	placebo-controlled, parallel group	controlled, parallel group
Phase	Phase 2b	Phase 3	Phase 3	Phase 1	Phase 1
Population	*Confirmed P. vivax* malaria	*Confirmed P. vivax* malaria	Confirmed P vivax malaria	Healthy subjects	Healthy subjects
Age group	≥ 16 years	≥ 16 years	≥ 16 years	18 to 45 years	18 to 65 years
No. subjects, N	329	522	251	164	208
Treatment Groups	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)	At interim: TQ 300 mg + CQ (n=110) CQ alone (n=54)	TQ 300 mg (n=52) TQ 600 mg (n=52) TQ 1200 mg Moxifloxacin (n=52) Placebo (n=52)
Primary Objective	Efficacy	Efficacy	Occurrence of hemolysis	Ophthalmologic effects	Effects on QT interval
Study Duration (days)	180	180	180	120	96
Study Status	Completed	Completed	Completed	Ongoing	Completed

*Study 201807 is on-going and interim results were submitted in the original NDA submission, as agreed with the applicant. Planned enrollment, n= 300.
Source: Adapted from NDA 210-795: Applicant's Summary of Clinical Safety, Module 2.7.4., Table 1.

Exposure to TQ 300mg single-dose

The safety population exposed to TQ 300mg single-dose in the three key trials TAF 112582 part 1 & 2 and TAF116564 is summarized in Table 49. In the two placebo-controlled trials, TAF 112582 part 1 & 2, 317 patients were exposed to TQ 300 mg single-dose + CQ, 187 patients were exposed to CQ, and 179 patients were exposed to PQ+CQ.

In TAF 112582 part 1 & 2 and TAF116564, 483 patients were exposed to TQ 300mg + CQ and 264 patients were exposed to PQ + CQ. CQ plus PQ x 14 days is the current standard of care for treatment of CQ-sensitive *P. vivax* malaria and is an appropriate comparator regimen to use as a benchmark.

Table 49. TAF112582 & TAF116564: Exposure to TQ 300 mg single-dose in patients with *P. vivax* malaria

Clinical Trial	Treatment Arms		
	TQ 300mg + CQ	PQ 15mg + CQ	CQ
Study TAF112582, Part 1*	57	50	54
Study TAF112582, Part 2	260	129	133
Study TAF116564	166	85	NA
Total no. patients	483	264	187

NA: Not applicable
* Data for doses of TQ other than 300mg are omitted.
Source: NDA 210795, demographic dataset, JReview v. 11.0

Relevant characteristics of the safety population

The safety population included all randomized subjects who received at least one dose of TQ. It included male and female patients 15 to 75 years of age with confirmed *P. vivax* malaria based on reading of a blood smear. The average age of study subjects was 35 years and 75% were male. Approximately 2% of the population were > 65 years of age. Demographic characteristics of patients in TAF 112582 part 1 and TAF 112582 part 2 are summarized in Table 19, Table 20, Table 27, and Table 28.

In TAF112582 part 1 & 2, study sites were located across three continents in Brazil, Peru, Philippines, Thailand, Cambodia, India, and Ethiopia. The highest enrolling sites were in Brazil (33%), Peru (33%), and Thailand (16%). Race is often difficult to classify in South America and many subjects in Brazil were of mixed descent. The large proportion of subjects (36%) of American Indian race were at sites in Peru and Brazil in TAF112582 part 2.

Adequacy of the Safety Database

The safety database of 810 subjects exposed to TQ 300mg single-dose appears adequate to assess its safety as a treatment for radical cure of *P. vivax* malaria. Limited safety data are also available for higher single-doses of TQ, 600mg and 1200mg in the Thorough QT (TQT) study, TAF114582.

9.1.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality of the NDA is satisfactory and there are no concerns related to data integrity. The applicant included statements of Good Clinical Practice (GCP) for each trial.

Categorization of Adverse Events

The method for collecting adverse event data was predefined in the study protocols for each of the three key clinical trials, TAF112582 part 1 & part 2 and TAF116564. Information on adverse events were documented in case report forms by the investigators. Adverse events (AEs) were

coded using Medical Dictionary for Regulatory Activities (MedDRA) as follows: TAF112582, part 1 used MedDRA v.16.0; TAF112582, part 2 and TAF 116564 used MedDRA v.19.1. The Integrated Summary of Safety (ISS) used MedDRA v.20.0.

A treatment emergent adverse event (TEAE) was defined as an AE with a start date on or after the date of the first dose of study medication up to and including Day 180 for the three primary trials described in Table 48.

- A serious adverse event (SAE) was defined as per regulations, 21CFR312.32
- Events of possible drug-induced liver injury with hyperbilirubinemia were defined as ALT ≥3x ULN and bilirubin ≥2x ULN (>35% direct) (or ALT ≥3x ULN and INR >1.5, if INR measured) termed 'Hy's Law' events.
  NOTE: Bilirubin fractionation was performed if testing was available. If testing was unavailable, presence of detectable urinary bilirubin on dipstick was recorded indicating direct bilirubin elevations and suggesting liver injury. If testing was unavailable and a subject met the criterion of total bilirubin ≥2x ULN, then the event was still reported as an SAE. If an INR was obtained, values were included on the SAE form. INR elevations >1.5 suggested liver injury.
- A protocol specified hematologic SAE was defined as a decrease in hemoglobin >3.0 g/dL or ≥30% from baseline in TAF112582 part 2. The cut-off was lower in TAF112582 part 1 i.e., a decrease of >2.5 g/dL or ≥ 25% from baseline Hgb) or an overall decrease in hemoglobin to below 6.0 g/dL in the first 15 days of the study.

Clinical Reviewer's Comment: The coding of AEs from the reported terms to MedDRA dictionary derived terms was reviewed for TAF112582 part 1 & part 2 and TAF116564 and was found acceptable.

Routine Clinical Tests

Routine clinical evaluations for safety included a medical history for assessment of symptoms of AEs, vital sign measurements and physical examinations for assessment of signs of AEs, clinical laboratory tests, and ECGs. In phase 3 trials, evaluations were performed at baseline, and on Days 2, 3, 8, 11, 15, 22, 29, 60, 90,120, 150, and 180. Subjects who discontinued treatment prematurely due to AEs were to attend all follow-up visits through Day 180. Patients with relapse (positive blood smear for *P. vivax*) were monitored at all scheduled visits through Day 180.

9.1.4.Safety Results

Deaths

There were no deaths in the TQ clinical development program. No patients were withdrawn from the studies due to an AE. SAEs occurred at similar rates at < 10% across treatment arms, TQ+CQ, PQ+CQ, and CQ, (Table 50). AEs leading to discontinuation of one of the drugs to which they were randomized occurred in ≤ 3% of patients.

Table 50. TAF112582 & TAF116564: Overview of Adverse Events

ADVERSE EVENTS	TAF112582, Part 1 & Part 2	TAF112582 & TAF116564

	N=683			N=747	
	TQ 300mg+CQ N=317 n (%)	PQ +CQ N=179 n (%)	CQ N=187 n (%)	TQ 300mg + CQ N=483 n (%)	PQ+ CQ N=264 n (%)
AEs	202(64%)	108(60%)	127(68%)	321(66%)	172(65%)
SAEs	23(7%)	11(6%)	10(5%)	29(6%)	12(5%)
Deaths	0	0	0	0	0
AE leading to withdrawal from study	0	0	0	0	0
AE leading to discontinuation of drugs	12(4%)	1(0.6%)	6(3%)	13(3%)	2(0.7%)

AEs: Adverse events; SAEs: Serious adverse events.
Source: NDA 210795, ISS, Adverse event dataset (ADAE). JReview 11.0

Serious adverse events

Decreases in Hgb levels and prolongation of the QT interval were the most common SAEs observed in the placebo-controlled trials, TAF 112582 part 1 & 2.

Decreases in Hgb levels were reported in 14 (4.4%) patients and it was the only SAE (pre-specified in protocols) reported in more than one subject in the TQ 300mg +CQ treatment group. Asymptomatic prolongation of the QTcF interval was the only SAE reported in more than one subject in the PQ+CQ (n=4, 2.2%) and the CQ (n=5, 2.7%) treatment groups. One case of acute hepatitis and a possible case of drug-induced liver injury reported with TQ+CQ and PQ+CQ, respectively, are further discussed in section 9.1.5.

SAEs for the TQ 300mg + CQ groups in the placebo (CQ)-controlled trials, TAF 112582 part 1 & 2 are summarized by system organ class in Table 51.

Table 51. TAF112582 Part 1 and 2: Serious adverse events - Safety population

		Treatment Arm					
		300mg TQ sd		15mg PQ od x14d		CQ x 3d	
		N=317		N=179		N=187	
System Organ Class	**Preferred Term**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Investigations	Hemoglobin decreased	14	4.4%	3	1.7%	3	1.6%
	Electrocardiogram QT prolonged	1	0.3%	4	2.2%	5	2.7%
	Alanine aminotransferase increased	.	.	.	.	1	0.5%
Gastrointestinal disorders	Diarrhea	1	0.3%	1	0.6%	.	.
	Nausea	.	.	1	0.6%	.	.
	Vomiting	.	.	1	0.6%	.	.
Infections and infestations	Abscess limb	1	0.3%	.	.	.	.
	Gastroenteritis	.	.	.	.	1	0.5%
	Hepatitis E	1	0.3%	.	.	.	.
	Urinary tract infection	1	0.3%	.	.	.	.

		Treatment Arm					
		300mg TQ sd		15mg PQ od x14d		CQ x 3d	
		N=317		N=179		N=187	
System Organ Class	**Preferred Term**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Blood and lymphatic system disorders	Anemia	1	0.3%	.	.	.	.
	Methemoglobinemia	.	.	1	0.6%	.	.
Hepatobiliary disorders	Drug-induced liver injury	1	0.3%	.	.	.	.
	Hepatitis acute	.	.	1	0.6%	.	.
Metabolism and nutrition disorders	Dehydration	.	.	1	0.6%	.	.
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	1	0.3%	.	.	.	.
Reproductive system and breast disorders	Menorrhagia	1	0.3%	.	.	.	.

AEBODSYS: system organ class; AEDECOD: MedDRA preferred term; sd: single dose; d: days;
Note: Subject (b) (6) (TQ600mg +CQ) in TAF112582, part1 experienced depression, see case narrative in section 9.1.5.
Source: NDA 210795, study TAF112582 part 1 and 2, pooled ADSL and ADAE datasets, JUMP Clinical v.12.2.0

In study TAF112582 part 1 &2, three pregnancies were reported.

In study TAF112582 part 2, Subject (b) (6) had a positive pregnancy test approximately 12 days after the start of study medication (study Day 13). She had a documented negative pregnancy test at screening and started study drug on Day 2. She states that she was compliant with oral contraceptives which she started on study Day 5. Study drugs were discontinued following confirmation of the pregnancy. The subject had a spontaneous abortion (SAE) confirmed on Day 31. A uterine curettage was performed on study Day 33. At the time of reporting, the subject was well and the adverse event had fully resolved. An association between study drugs and the spontaneous abortion cannot be ruled out.

Subject (b) (6) had a positive pregnancy test on an unspecified date after the start of study medication. She subsequently withdrew consent and was lost to follow-up. At the time of reporting, the outcome of the pregnancy was unknown.

In study TAF112582 part 1, Subject (b) (6) in the TQ 100mg + CQ group had a negative screening test prior to study drug administration and a positive pregnancy test two weeks post treatment. The patient did not use contraception. She had an elective abortion one month later. No further follow up was provided.

Dropouts and/or Discontinuations Due to Adverse Events

No AEs resulted in withdrawal of patients from the placebo-controlled trials (pooled TQ 300mg + CQ, PQ+CQ, and CQ treatment arms). Eleven (3.5%) patients in the TQ 300mg + CQ group and 2 (1.1%) patients in the CQ group who experienced decreases in Hgb >3g/dL levels (pre-

specified SAE) post baseline were discontinued from the study drugs, (see Table 52). These cases are discussed in Section 9.1.5.

One patient in the TQ 300mg + CQ group had mixed *P. falciparum and P. vivax* infection, a decrease in Hgb of 3g/dL from baseline, and evidence of splenomegaly at enrollment. TQ + CQ were stopped and the patient was treated with artemether/lumefantrine.

No patient in the TQ 300mg + CQ group experienced QTc prolongation. A higher proportion of subjects in the CQ group (n=4, 2%) had QTc prolongation on ECG leading to discontinuation of study drugs compared to the other treatment groups (<1%).

Table 52. TAF112582 part 1 & 2: Treatment Emergent Adverse Events Leading to Discontinuation of Study Drugs – Safety Population

Adverse Events	TQ 300mg + CQ N = 317 N (%)	CQ N = 187 N (%)	PQ + CQ N = 179 N (%)
Hemoglobin decreased	11 (3.5)	2 (1.1)	0
P. falciparum and *P. vivax* infection	1	0	0
QTc Prolongation	0*	4 (2.1)	1 (0.6)

*In study TAF112582, part 1, one patient in the TQ 50mg + CQ group withdrew from study drugs due to asymptomatic QTcF interval prolongation. No patient in the TQ 100mg + CQ or TQ 600mg + CQ had QTc prolongation. Source: NDA 210795, study TAF112582 part 1 & 2, ADSL and ADAE datasets, JReview v. 11.0

Clinical reviewer's comment: Hemolysis and hemolytic anemia in G6PD deficient patients are known side-effects of PQ. Other hematologic adverse reactions such as pancytopenia, agranulocytosis, and aplastic anemia have been reported with CQ and MQ, although these adverse reactions are rare. Hgb decreases in G6PD-normal individuals are expected to be less frequent and less severe than in G6PD deficient individuals.

QTc prolongation is listed in the Precautions section of the labeling for the 8-aminoquinoline, PQ, and in the Warnings section for the 4-quinolinemethanol, MQ. QT prolongation is not listed as an AE in the chloroquine phosphate labeling but has been documented in a healthy volunteer study comparing CQ to another aminoquinoline AQ13.[20] QT prolongation has also been associated with chronic use of hydroxychloroquine.[21]

Significant Adverse Events

An evaluation of reported AEs according to CDER's list of Designated Medical Events (DME) was performed to identify subjects who experienced one of the following: acute pancreatitis, acute respiratory failure, agranulocytosis, anaphylaxis or anaphylactoid reaction, aplastic anemia,

[20] Mzayek F, Deng H, Mather FJ, et al. Randomized dose-ranging controlled trial of AQ-13, a candidate antimalarial and chloroquine in healthy volunteers. PLoS Clin Trials 2007; 2: e6

[21] Hydroxychloroquine (Plaquenil®): https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5f5f1dee-854a-41f6-b304-d7fdf8dd3ea0

blindness, bone marrow depression, deafness, disseminated intravascular coagulation, hemolytic anemia, liver failure, liver necrosis, liver transplant, pancytopenia, renal failure, seizure, Stevens-Johnson syndrome, torsades de pointes, toxic epidermal necrolysis, thrombotic thrombocytopenic purpura, and ventricular fibrillation. DMEs are AEs reflecting serious medical conditions that may be related to drugs. All DMEs from TAF112582 part 1&2, TAF116564, TAF114582 (TQT study), 201807(ophthalmology safety study in healthy subjects) and TAF110027 (G6PD-normal and G6PD deficient healthy subjects) were reviewed.

Two cases of hypersensitivity were reported with a single dose of TQ in study TAF114582 (TQT study) and one case report of hypersensitivity was reported with CQ in study TAF112582. Symptoms and signs included shortness of breath, lip swelling, swelling of the throat, pruritus, and diffuse urticaria. The case narratives for the two patients who received TQ are described below.

• A 45-year-old female (# (b) (6), site (b) (6)) experienced severe allergic reaction 13 days (study Day 18) after receiving a single dose of TQ 300 mg. The patient was randomized to receive placebo on Day 1 and 2, and TQ 300 mg and placebo on Day 3. Concomitant medications included Advair® (fluticasone propionate + salmeterol), salbutamol sulfate, and budesonide. The subject experienced shortness of breath, lip swelling, itchiness, and diffuse hives. Her symptoms were relieved by diphenhydramine and an unnamed nebulized treatment. In addition, she had attended the Emergency Department on the previous day for the same complaint and was treated with prednisone, diphenhydramine, and famotidine. She remained on the study and the SAE resolved within 7 days. The SAE was considered by the investigator to be possibly related to TQ. The case report suggested that shortness of breath was confounded by an undisclosed past medical history of asthma.

Clinical Reviewer's Comment: *The episode of shortness of breath occurred concurrently with lip swelling, itchiness, and diffuse urticaria indicating a hypersensitivity reaction, therefore it is not considered to be confounded by this reviewer. The adverse event does not meet the criteria for anaphylaxis due to the delayed onset of symptoms 13 days following administration of study drugs.[22] The DPARP consult review for this case noted that the duration of symptoms for several days is inconsistent with anaphylaxis, (see consult review, 5/15/2018, by Dr. J. Lan in DARRTS). There were no other documented triggers and there is a reasonable possibility that this case represents hypersensitivity to TQ. The prolonged duration of symptoms (7 days) is probably due to the long half-life of TQ (~ 15 days).*

• A 23-year-old female (# (b) (6), site (b) (6)) experienced an allergic reaction 15 days (study Day 17) after receiving TQ 600 mg single dose. The subject was randomized to receive placebo on Day 1 and 2, and TQ 600 mg and placebo on Day 3. The subject initially started itching and developed difficulty in swallowing, swelling of throat, some swelling of the hands and feet, and sudden appearance of hives all over her body. The subject was treated with diphenhydramine, methylprednisolone, and triamcinolone cream. She remained in the study. The difficulty swallowing and swelling of the throat resolved within one hour. The swelling of the hands and

feet persisted for two days, and the hives persisted for four days. An immunologist diagnosed allergic urticaria due to study drug or antecedent viral upper respiratory infection.

Clinical reviewer's comment: The duration of intermittent symptoms lasting four days is not consistent with anaphylaxis.[22] The DPARP consult reviewer noted that given the patient's preceding viral illness, the hives and angioedema were likely viral-induced; however, a TQ-induced hypersensitivity cannot be excluded, (see consult review, 5/15/2018, by Dr. J. Lan), in DARRTS.

One additional report of hypersensitivity occurred in a 21y male patient [# (b) (6) / site (b) (6)] who received CQ in TAF112582, part 1. The patient developed rash, wheezing, and abdominal pain 12 hours after a single-dose of CQ 600 mg. The patient had no history of allergies or concomitant medications. This patient recovered following treatment with an antihistamine, prednisone, and a bronchodilator. This patient was a screen failure, CQ was discontinued. He was withdrawn from the trial and treated with artemether-lumefantrine.

Clinical Reviewer's Comment: Hypersensitivity reactions were associated with TQ alone and with CQ alone. The clinical reviewer agrees with the Applicant's proposal to include hypersensitivity in the WARNINGS section of the TQ label.

Allergic reactions have been reported for quinoline anti-malarial drugs. In the PQ phosphate USPI, rash and pruritus are listed under the Adverse Reactions section. Pruritus, urticaria, anaphylactic/anaphylactoid reaction and angioedema are listed in the Adverse Reactions section of the CQ phosphate USPI. The mefloquine hydrochloride USPI lists "hypersensitivity" in the Precautions section: "Hypersensitivity reactions have been reported with mefloquine use". The adverse reactions section lists: rash, exanthema, erythema, urticaria, pruritus, edema, erythema multiforme, and Stevens-Johnson syndrome, dyspnea, and pneumonitis of possible allergic etiology.

Treatment Emergent Adverse Events

Common treatment emergent adverse events (TEAEs) occurring at ≥ 1.0% in TAF112582 part 1 & 2 (pooled TQ 300mg + CQ, PQ+CQ and CQ treatment arms) up to Day 180 are summarized in Table 53.

Gastrointestinal disorders, nervous system, skin and soft tissue disorders, and infections and infestations were the most frequently affected system organ classes in the TQ + CQ -treated patients. Common adverse reactions occurring at ≥ 2 % in the TQ 300mg + CQ group and at a rate greater than CQ alone included: nausea (8%), vomiting (8%), diarrhea (6%), dizziness (10%),

[22] Sampson, H., Muñoz-Furlong, A., Campbell, R., et al. Second symposium on the definition and management of anaphylaxis: Summary Report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006; 117:391-397.

viral upper respiratory tract infection (6%), pharyngitis (5%), Hgb decreased (5%), insomnia (4%), and back pain (5%). Elevations in ALT (3%) and CPK (4%) were observed in patients treated with TQ + CQ but at lower rates than in the CQ group. Pruritus was reported across all treatment groups, in 42 (13%) patients in the TQ 300mg +CQ group, 27 (14%) patients in the CQ group, and 17 (10%) patients in the PQ+CQ group. Pruritus was not associated with other symptoms of allergy. The incidence of pruritus in the TQ 300mg+ CQ arm was similar to the incidence reported for the CQ only arm. Dizziness, decreases in hemoglobin, and insomnia are discussed in more detail in section 9.1.5.

Table 53. TAF112582 part 1 & 2: Treatment emergent adverse events in ≥ 1.0% subjects by treatment group - Safety population

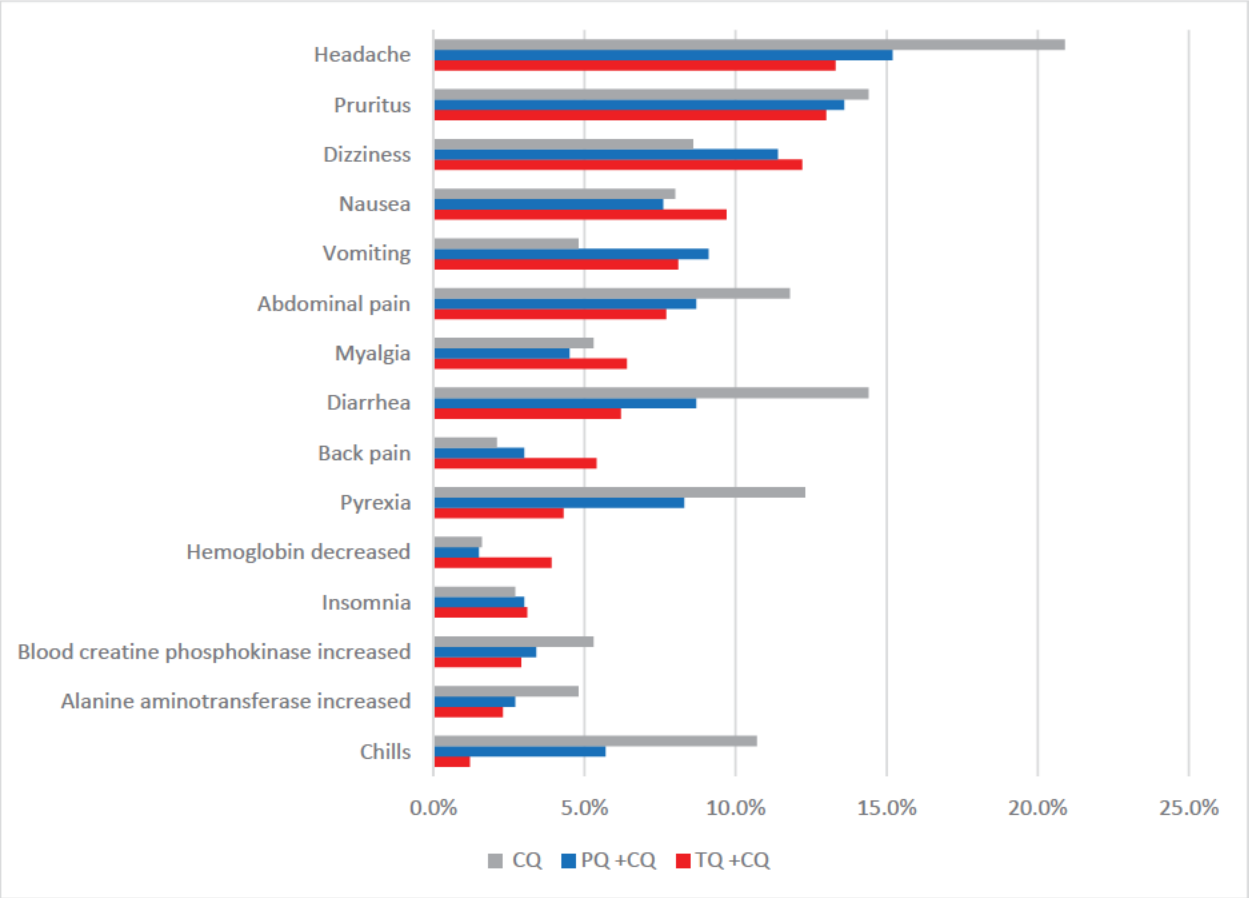
		Treatment Arm					
		TQ 300mg sd + CQ		CQ x 3d		PQ 15mg od x14d + CQ	
		N=317		N=187		N=179	
System Organ Class	**Preferred Term**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Gastrointestinal disorders	Nausea	26	8.2%	15	8.0%	13	7.3%
	Abdominal pain upper	17	5.4%	18	9.6%	14	7.8%
	Vomiting	24	7.6%	9	4.8%	16	8.9%
	Diarrhea	18	5.7%	10	5.3%	9	5.0%
	Abdominal pain	8	2.5%	9	4.8%	7	3.9%
	Dyspepsia	6	1.9%	6	3.2%	3	1.7%
Nervous system disorders	Headache	37	11.7%	39	20.9%	24	13.4%
	Dizziness	30	9.5%	16	8.6%	14	7.8%
Infections and infestations	Viral upper respiratory tract infection	19	6.0%	9	4.8%	12	6.7%
	Pharyngitis	15	4.7%	7	3.7%	11	6.1%
	Urinary tract infection	12	3.8%	9	4.8%	7	3.9%
	Gastroenteritis	6	1.9%	3	1.6%	2	1.1%
	Oral herpes	6	1.9%	1	0.5%	2	1.1%
	Parasitic gastroenteritis	5	1.6%	2	1.1%	2	1.1%
	Fungal skin infection	2	0.6%	4	2.1%	1	0.6%
General disorders and administration site conditions	Pyrexia	14	4.4%	23	12.3%	16	8.9%
	Chills	6	1.9%	20	10.7%	12	6.7%
	Asthenia	3	0.9%	4	2.1%	.	.
Investigations	Blood creatine phosphokinase increased	11	3.5%	10	5.3%	7	3.9%
	Alanine aminotransferase increased	10	3.2%	9	4.8%	7	3.9%
	Hemoglobin decreased	15	4.7%	3	1.6%	3	1.7%
	Electrocardiogram QT prolonged	3	0.9%	7	3.7%	5	2.8%
Musculoskeletal and	Myalgia	16	5.0%	22	11.8%	12	6.7%

		Treatment Arm					
		TQ 300mg sd + CQ		CQ x 3d		PQ 15mg od x14d + CQ	
		N=317		N=187		N=179	
System Organ Class	**Preferred Term**	**Count**	**%**	**Count**	**%**	**Count**	**%**
connective tissue disorders							
	Back pain	17	5.4%	4	2.1%	5	2.8%
	Arthralgia	5	1.6%	3	1.6%	2	1.1%
Skin and subcutaneous tissue disorders	Pruritus	42	13.2%	27	14.4%	17	9.5%
Psychiatric disorders	Insomnia	13	4.1%	5	2.7%	8	4.5%
Respiratory, thoracic and mediastinal disorders	Cough	5	1.6%	4	2.1%	6	3.4%
	Rhinorrhea	6	1.9%	3	1.6%	2	1.1%
Eye disorders	Vision blurred	3	0.9%	4	2.1%	3	1.7%

Source: NDA 210795, study TAF 112582 part 1 & 2, ADSL and ADAE datasets, JUMP Clinical v. 12.2.0

Treatment Emergent Adverse Events (TEAEs) in Studies TAF112582 part 1&2 and TAF116564.
Select TEAES from the pooled clinical trials by treatment arms, TQ 300mg + CQ (N=483), PQ+CQ (N=264) and CQ (N=187), and are summarized in Figure 5. TEAEs such as headache, pruritus, and dizziness were common across the 3 treatment groups. Headache was more common in the CQ group.
Dizziness, nausea, vomiting, and decreases in hemoglobin levels were more common in the TQ 300mg +CQ group than the CQ group suggesting an association with TQ. There were not enough data to associate backpain or myalgia with the study drugs. Insomnia occurred at similar rates (~3%) across the three treatment groups.

Figure 5. Study TAF112582 part 1 and 2 and Study TAF116564: Select TEAEs



Note: TQ+CQ = TQ 300mg + CQ;
Source: NDA 210795: ADAE dataset. Graph constructed in Microsoft Excel 2016

Clinical reviewer's comment: Pruritus is a known adverse reaction associated with CQ and is the likely cause of pruritus in the trials. TQ or PQ did not appear to exacerbate pruritus. In study TAF112582 part 1, in which subjects received ascending doses of TQ 50mg to 600mg, pruritus was observed but was not dose-related, TQ 50mg + CQ (7%), TQ 100mg + CQ (14%), TQ 300mg + CQ (14%) and TQ 600mg + CQ (4%). Headache, pyrexia, and chills were more frequent in the CQ group and were probably associated with the higher rate of P. vivax recurrences in this group.

Adverse events occurring in the first month post treatment

Adverse events occurring in the first month post dosing are more likely to be related to study drugs and were evaluated through Day 29 (visit # 100) in a separate analysis, (Table 54). Most of the adverse events in the trials occurred during the first month post treatment. Gastrointestinal disorders were the most common adverse events. Adverse events occurring at a rate ≥ 2% in the TQ+CQ group and at a rate greater than the CQ group, respectively included: dizziness (8% vs. 3%), vomiting (5% vs. 4%), Hgb decreased (5% vs. 2%), insomnia (4% vs. 3%), and backpain (3% vs.1%).

Table 54**. TAF112582 part 1 and 2: Treatment Emergent Adverse Events occurring in ≥ 2% of patients with onset on or prior to Day 29**

		Treatment Arm					
		TQ 300mg sd		CQ x 3d		PQ 15mg od x14d	
		N=317		N=187		N=179	
System Organ Class	**Preferred Term**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Gastrointestinal disorders	Nausea	20	6.3%	12	6.4%	8	4.5%
	Abdominal pain upper	13	4.1%	14	7.5%	12	6.7%
	Vomiting	17	5.4%	7	3.7%	10	5.6%
	Diarrhea	13	4.1%	7	3.7%	6	3.4%
	Abdominal pain	6	1.9%	6	3.2%	4	2.2%
	Dyspepsia	4	1.3%	4	2.1%	3	1.7%
Skin and subcutaneous tissue disorders	Pruritus	37	11.7%	24	12.8%	17	9.5%
Nervous system disorders	Dizziness	25	7.9%	6	3.2%	10	5.6%
	Headache	15	4.7%	12	6.4%	9	5.0%
Investigations	Alanine aminotransferase increased	8	2.5%	7	3.7%	6	3.4%
	Hemoglobin decreased	15	4.7%	3	1.6%	3	1.7%
	Blood creatine phosphokinase increased	8	2.5%	6	3.2%	1	0.6%
	Electrocardiogram QT prolonged	3	0.9%	7	3.7%	5	2.8%
Infections and infestations	Urinary tract infection	8	2.5%	6	3 2%	3	1.7%
	Pharyngitis	5	1.6%	5	2.7%	4	2.2%
	Viral upper respiratory tract infection	3	0.9%	1	0.5%	3	1.7%
Psychiatric disorders	Insomnia	12	3.8%	5	2.7%	8	4.5%
Musculoskeletal and connective tissue disorders	Back pain	9	2.8%	2	1.1%	1	0.6%

AEBODSYS: Body System Organ Class; AEDECOD: preferred term;
Source: NDA 210795, Study TAF112582 part 1 & 2, ADSL and ADAE datasets, JUMP Clinical v. 12.2.0

Clinical Reviewer's Comment: *Dizziness, vomiting, Hgb decreased, and insomnia are considered related to TQ and are known side effects of other quinoline antimalarials.*

Severity of Treatment Emergent Adverse Events

Adverse events ≥ grade 3 severity were uncommon in the two placebo-controlled efficacy trials. One subject in the TQ 300mg+CQ treatment group had a spontaneous abortion at six weeks' gestation (Grade 5); the Grade 5 severity refers to death of the embryo. The spontaneous abortion was considered not related to study drugs by the investigator and the subject was well at the time of reporting.

Four (2.2%) patients in the CQ only treatment group developed reversible QTc prolongation on ECG as compared to zero subjects in the TQ 300mg + CQ group. Two (1.1%) subjects in the CQ

only group and 1(0.6%) subject in the PQ+CQ treatment group developed Grade 4 QTc prolongation on ECG. All patients were asymptomatic and all recovered, Table 55).

Table 55. TAF112582 part 1 and 2: Treatment Emergent Adverse Events at Toxicity Grade ≥ 3

		CQ x 3d		PQ 15mg od x14d		TQ 300mg sd	
		N= 187		N=179		N=317	
System Organ Class	**Preferred Term**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Toxicity Grade 3:							
Investigations	Electrocardiogram QT prolonged	2	1.1%	1	0.6%	.	.
	Alanine aminotransferase increased	1	0.5%	.	.	.	.
	Aspartate aminotransferase increased	.	.	.	.	1	0.3%
	Blood creatine phosphokinase increased	1	0.5%	.	.	.	.
General disorders and administration site conditions	Chills	1	0.5%	1	0.6%	.	.
	Pyrexia	1	0.5%	1	0.6%	.	.
Infections and infestations	Abscess limb	.	.	.	.	1	0.3%
	Hepatitis E	.	.	.	.	1	0.3%
Gastrointestinal disorders	Diarrhea	.	.	1	0.6%	.	.
Musculoskeletal and connective tissue disorders	Myalgia	.	.	1	0.6%	.	.
Skin and subcutaneous tissue disorders	Pruritus	.	.	.	.	1	0.3%
Toxicity Grade 4 or 5:							
Investigations (grade 4)	Electrocardiogram QT prolonged	2	1.1%	1	0.6%	.	.
Pregnancy, puerperium, perinatal (grade 5)	Spontaneous abortion	.	.	.	.	1	0.3%

AEBODSYS: Body System Organ Class; AEDECOD: MedDRA preferred term;
Source: NDA 210795, Study TAF112582 part 1 & 2, ADSL and ADAE datasets, JUMP Clinical v. 12.2.0

Adverse Events leading to Withdrawal

No subject had AEs that led to withdrawal from the phase 2b/3 trials, TAF112582 part 1 & 2 and TAF116564.

Laboratory Findings

A summary of chemistry and hematology laboratory data of clinical concern at any time while on study in TAF112582 part 1 and 2 is presented in Table 56 and Table 57.

Chemistry Laboratory Tests
Elevations in chemistry parameters occurred at similar rates across the three treatment groups. Elevations of indirect bilirubin, a feature of red cell lysis and hemolytic anemia, was present in <10% of subjects in the three treatment arms. Seven (2%) subjects in the TQ + CQ treatment group had CPK elevations > 5 x ULN during the study. Strenuous physical exercise was a cause in some of the patients; these cases are further discussed in section 9.1.5. Elevated bilirubin levels were present at baseline in some subjects with *P. vivax* malaria. Elevations in urea related to dehydration from malaria were present at baseline in subjects in all treatment groups.

Table 56. TAF112582, part 1 and 2: Chemistry laboratory results of potential clinical concern (placebo-controlled) - Safety population

Blood Lab Test	Category (Criteria)	TQ 300mg+CQ N=317; n(%)	CQ N=187; n(%)	PQ+CQ N=179; n(%)
ALT	High > 3xULN	14 (4)	14 (7)	7 (4)
AST	High > 3xULN	10 (3)	6 (3)	3 (2)
Alk phosphatase	High > 2.5xULN	1 (<1)	4 (2)	1 (<1)
Bilirubin	High > 1.5xULN	31 (10)	23 (12)	18 (10)
Indirect bilirubin	High > 1.5xULN	28 (9)	16 (9)	11 (6)
CPK	High > 5xULN	7 (2)	12 (6)	9 (5)
Creatinine	High > 3xULN	1 (<1)	0	0
eGFR	Low (< 0.4843mL /sec/1.73m^2)	2 (<1)	0	0
Urea	High (> 11.067 mmol/L	93 (29)	47 (25)	52 (29)

Source: NDA 210795, ISS, adapted from Applicant's Table 39 and Table 11.068.
The Applicant noted that a value of 11.067 mmol/L was used as a cut-off for values of clinical concern, which was lower than the upper limit of normal for two sites in Brazil.

Hematology Laboratory Tests
The proportions of subjects with abnormal values in any hematology parameter were similar across treatment groups, except for increases in methemoglobin percentage (MetHb%) and reticulocyte counts. Elevations in reticulocyte counts were associated with decreases in Hgb levels. In general, platelet concentrations were high in all treatment groups at baseline and decreased over time to within the normal range. Elevated eosinophil counts were observed in some subjects, which may be related to the history of helminthic infections reported in similar proportions of subjects across all three treatment groups. Elevated eosinophil counts were more frequent in the PQ+CQ (25%) group compared to TQ+CQ (17%). Hematologic parameters such as decrease in Hgb level are discussed in more detail in section 9.1.5.

Table 57. TAF112582 part 1 & 2: Hematologic laboratory results of potential clinical concern - Safety population

Laboratory Test	Category (Criteria)	TQ 300mg+CQ N=317; n(%)	CQ N=187; n(%)	PQ+CQ N=179; n(%)

Laboratory Test	Category (Criteria)	TQ 300mg+CQ N=317; n(%)	CQ N=187; n(%)	PQ+CQ N=179; n(%)
Eosinophils	High > 1.5x10^9/L	53 (17)	38 (20)	44 (25)
Leukocytes	High > 2x x10^9/L	3 (< 1)	0	2 (1)
Lymphocytes	Low > 0.5 x10^9/L; High > 4 x10^9/L	4 (1); 44 (14)	8 (4); 31 (17)	2(1); 22(12)
Neutrophils	< 1.0 x x10^9/L	6 (2)	4 (2)	7(4)
Platelets	Low (< 50X10^9/L)	42 (13)	19 (10)	21(12)
Reticulocytes	High (> 1.0xULN)	170 (54)	100 (53)	112(63)
Methemoglobin	High (> 10%)	8 (3)	8 (4)	20(11)

Source: NDA 210795, ISS adapted from Applicant's Table 40 and Table 11.070.

Clinical Reviewer's Comment: *Pseudo-eosinophilia due to hemozoin-containing neutrophils is seen in malaria and could be a factor in the eosinophilia that was observed across the three treatment arms.*[23]

In TAF112582, part 2, clinical chemistry tests included CPK, BUN, serum creatinine, total and indirect bilirubin, and hepatic transaminases. Elevations in hepatic enzymes, ALT, AST and total bilirubin from baseline were grade 1 or 2 in severity in most patients and occurred at a similar frequency in the three treatment groups, (Table 58). Grade 3 elevations in hepatic enzymes or total bilirubin occurred in < 3% of subjects in the TQ 300mg + CQ group. Hepatic adverse events are discussed in greater detail in section 9.1.5.

Table 58. TAF112582, part 2: Hepatic Laboratory Tests – Baseline vs. Max. Toxicity Grade

Test	Baseline Grade	Maximum Grade Post Baseline	TQ+CQ N=260	CQ N=133	PQ+CQ N=129
ALT Incr	**Grade 0**	**Grade 0**	**153 (58.8%)**	**59 (44.4%)**	**64 (49.6%)**
		Grade 1	80 30.8%)	58 (43.6%)	52 (40.3%)
		Grade 2	3 (1.2%)	2 (1.5%)	4 (3.1%)
		Grade 3	4 (1.5%)	0	0
	Grade 1	Grade 0	9 (3.5%)	3 (2.3%)	5 (3.9%)
		Grade 1	56 21.5%)	24 (18.0%)	26 (20.2%)
		Grade 2	3 (1.2%)	7 (5.3%)	0
		Grade 3	1 (0.4%)	3 (2.3%)	1 (0.8%)
	Grade 2	Grade 1	1 (0.4%)	0	0
		Grade 3	0	1 (0.8%)	1 (0.8%)
AST Incr	**Grade 0**	**Grade 0**	**145 (55.8%)**	**64 (48.1%)**	**76 (58.9%)**
		Grade 1	61 (23.5%)	47 (35.3%)	28 (21.7%)
		Grade 2	2 (0.8%)	1 (0.8%)	0
		Grade 3	3 (1.2%)	0	0
	Grade 1	Grade 0	15 (5.8%)	1 (0.8%)	6 (4.7%)
		Grade 1	31 (11.9%)	16 12.0%)	17 (13.2%)
		Grade 2	1 (0.4%)	2 (1.5%)	1 (0.8%)

Test	Baseline Grade	Maximum Grade Post Baseline	TQ+CQ N=260	CQ N=133	PQ+CQ N=129
		Grade 3	0	2 (1.5%)	1 (0.8%)
	Grade 3	Grade 2	1 (0.4%)	0	0
BILI Incr	**Grade 0**	**Grade 0**	**182 (70.0%)**	**84 (63.2%)**	**93 (72.1%)**
		Grade 1	53 (20.4%)	31 (23.3%)	24 (18.6%)
		Grade 2	17 (6.5%)	16 (12.0%)	12 (9.3%)
		Grade 3	6 (2.3%)	1 (0.8%)	0
		Grade 4	0	1 (0.8%)	0
	Grade 1	Grade 0	43 (16.5%)	15 (11.3%)	20 (15.5%)
		Grade 1	17 (6.5%)	12 (9.0%)	9 (7.0%)
		Grade 2	5 (1.9%)	3 (2.3%)	5 (3.9%)
	Grade 2	Grade 0	26 (10.0%)	11 (8.3%)	15 (11.6%)
		Grade 1	14 (5.4%)	7 (5.3%)	8 (6.2%)
		Grade 2	5 (1.9%)	6 (4.5%)	4 (3.1%)
		Grade 3	2 (0.8%)	0	0
		Grade 4	0	1 (0.8%)	0
	Grade 3	Grade 0	0	0	1 (0.8%)
		Grade 1	2 (0.8%)	1 (0.8%)	0
		Grade 2	2 (0.8%)	5 (3.8%)	0
		Grade 3	3 (1.2%)	1 (0.8%)	0

Incr: increase. Source: TAF112582, part 2, ISS ADSL and ADAE datasets, JReview v. 11.0

In TAF 112582, part 2, elevations in serum creatinine where mild (grade 1) and occurred with a similar frequency across the three treatment groups (Table 59). Mild elevations in mean (SD) creatinine concentrations compared with baseline were noted in the TQ+CQ group at Day 5 (3.61±18.04 µmol/L) and Day 8 (2.95±19.73 µmol/L). TQ has inhibitory effects *in vitro* on the renal transporters OCT2, MATE1, and MATE2-K which might account for the increases in serum creatinine levels.

Table 59. TAF 112582, part 2: Renal Laboratory Tests - Toxicity Grades

Test	Baseline Grade	Maximum Grade Post Baseline	TQ 300mg + CQ N=260	CQ N=133	PQ+CQ N= 129
Creatinine Increase	**Grade 0**	**Grade 0**	**221 85.0%)**	**116 (87.2%)**	**115 (89.1%)**
		Grade 1	24 (9.2%)	11 (8.3%)	10 (7.8%)
		Grade 2	2 (0.8%)	0	1 (0.8%)
		Grade 3	1 (0.4%)	0	0
	Grade 1	Grade 0	5 (1.9%)	3 (2.3%)	0
		Grade 1	5 (1.9%)	2 (1.5%)	2 (1.6%)
		Grade 2	1 (0.4%)	0	1 (0.8%)

Source: NDA 210795, ADSL and ADAE datasets in ISS, JReview v. 11.0

Creatinine phosphokinase (CPK)

Clinically significant increases in serum CPK, grade 1, 2 grade 3 severity were observed throughout TAF 112582, part 2. There was overlap between subjects and toxicity grades, (Table 60).

Table 60. TAF 112582, part 2: Creatinine phosphokinase Laboratory Test – Toxicity Grades

Test	Baseline Grade	Maximum Grade Post Baseline	TQ 300mg +CQ N=260	CQ N=133	PQ+CQ N=129
CPK Increase	**Grade 0**	**Grade 0**	**181(69.6%)**	**87 (65.4%)**	**76 (58.9%)**
		Grade 1	53 (20.4%)	30 (22.6%)	41 (31.8%)
		Grade 2	3 (1.2%)	5 (3.8%)	7 (5.4%)
		Grade 3	2 (0.8%)	3 (2.3%)	1 (0.8%)
	Grade 1	Grade 0	7 (2.7%)	3 (2.3%)	1 (0.8%)
		Grade 1	9 (3.5%)	3 (2.3%)	2 (1.6%)
	Grade 2	Grade 0	0	2 (1.5%)	0
		Grade 1	3 (1.2%)	0	1 (0.8%)

Source: NDA 210795, ADSL and ADAE datasets in ISS, JReview v. 11.0

Vital Signs

There was no pattern of clinically significant changes in vital signs observed in any of the treatment groups in TAF112582 part 1 & 2.

Electrocardiograms (ECGs)

In TAF112582 parts 1 &2, there were no differences across the treatment groups in ECG assessments through 72 hours post-baseline. There were no subjects with clinically significant abnormal ECG findings in the TQ+CQ groups.

QT Interval

The QT-IRT consult review team found no significant effect of TQ on QTc interval in the Thorough QT clinical trial, TAF114582. The largest upper bounds of the 2-sided 90% CI for the mean difference between TQ at three dose levels (300 mg single dose, 600 mg single dose and 1,200 mg cumulative dose) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in the trial. Overall ECG acquisition and interpretation in this study was acceptable. There are no clinically meaningful effects on the PR and QRS intervals.

The Applicant included the following language in the proposed label:
12.2 Pharmacodynamics
Cardiac Electrophysiology
At a cumulative dose of 1,200 mg (400 mg/day for 3 days; 4 times the maximum recommended dose), TQ did not prolong the QT interval to any clinically relevant extent.

The following is QT-IRT's suggested revisions for section 12.2:
12.2 Pharmacodynamics
Cardiac Electrophysiology
The effect of TQ on the QTc interval was evaluated in a Phase 1 randomized, single-blind,

placebo and positive controlled, parallel-group thorough QTc study in 260 healthy adult subjects. (b) (4) recommended dose, TQ did not prolong the QTc interval to any clinically relevant extent.

Clinical Reviewer's Comment*: The clinical reviewer defers to the clinical pharmacology for a final decision on section 12.2 of the TQ package insert.*

Immunogenicity

Not applicable.

9.1.5.Analysis of Submission-Specific Safety Issues

Hematologic, neurologic, psychiatric, gastrointestinal, hepatobiliary, renal/urinary, and ophthalmologic treatment emergent adverse events in the TAF112582 part1 & 2 and TAF116564 are discussed in this section. Clinically significant laboratory abnormalities included mild to moderate grade decreases in Hgb levels, increases in MetHb% levels, increases in CPK levels, and mild to moderate increases in hepatic enzymes and bilirubin are also discussed.

Hematological Adverse Events

Drug-induced hemolysis is a safety concern with the 8-aminoquinoline class and is described in the PQ USPI. PQ is contraindicated in patients with severe G6PD deficiency.

In the three primary efficacy and safety trials, decreases in Hgb levels were more frequent in the patients treated with TQ 300mg + CQ (n=18, 3.7%) than patients treated with PQ + CQ (n=4, 1.5%) and CQ (n=3, 1.6%).

In study TAF116564, one patient in the TQ 300mg + CQ group developed grade 3 hyperbilirubinemia after Day 90 which does appear to be related to study drugs. All other AEs such as fatigue, dyspnea, tachypnea, and pallor which can be associated with anemia occurred at low rates of < 1.0% across the treatment arms, Table 61. One patient each in the TQ 300mg+CQ group, PQ+CQ group and CQ group experienced hyperbilirubinemia (grade 2 severity) and had increased levels of serum total and indirect bilirubin at baseline; the levels declined to normal ranges during the first week post treatment. Elevation of bilirubin levels from baseline occurred in one patient in the TQ+CQ group; it was probably related to P. *vivax* malaria; ALT levels were not significantly elevated.

Table 61. TAF112582 & TAF116564: Hematological Treatment Emergent Adverse Events

Preferred Term	TQ 300mg sd + CQ N = 483	CQ N = 187	PQ x 14d + CQ N =264
Anemia	1 (0.2%)	0	3 (1.1%)
Blood bilirubin increased	1 (0.2%)	NR	0
Dyspnea	2 (0.4%)	0	0
Fatigue	3 (0.6%)	2 (1.1%)	0
Hemoglobin decreased	18 (3.7%)	3 (1.6%)	4 (1.5%)

Preferred Term	TQ 300mg sd + CQ N = 483	CQ N = 187	PQ x 14d + CQ N =264
Hyperbilirubinemia	1 (0.2%)	1 (0.5%)	1 (0.4%)
Pallor	1 (0.2%)	0	0
Tachypnea	1 (0.2%)	0	0

Source: NDA 210795, ADSL and ADAE datasets in ISS, JReview v. 11.0

Clinical Reviewer's Comment: It is challenging to distinguish hemolysis due to P. vivax malaria from drug-induced hemolysis in the clinical trials. Anemia associated with malaria is multi-factorial and includes direct destruction of parasitized and non-parasitized red cells, splenic and hepatic sequestration and destruction of red cells, bone marrow suppression, and dyserythropoiesis. Decreases in Hgb levels occurred in patients with P. vivax malaria on treatment with TQ+CQ, PQ+CQ and CQ; however, decreases in Hgb levels occurred at a higher frequency in subjects treated with TQ 300mg + CQ (n=18, 3.7%) as compared to CQ alone (n=3, 1.6%), or PQ + CQ (n= 4, 1.5%) suggesting a higher risk of Hgb drops in subjects who received TQ 300mg + CQ. PQ can cause declines in Hgb in G6PD normal subjects which the Applicant suggested maybe be due to lysis of red blood cells approaching the end of their lifespan. In the clinical trials, rehydration may have contributed in part to the observed decreases in Hgb levels from baseline in some subjects because of increased intravascular volume. The data suggests that TQ+CQ is associated with decreases in Hgb levels in some G6PD normal subjects although there was no significant clinical or laboratory evidence of hemolysis.

Hematologic Adverse Events in the ISS database
The ISS database includes 33 clinical studies: Phase 1, 2, and 3 studies, single-dose and multiple -dose studies, studies in fasted and non-fasted subjects, bioavailability studies of 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). In the ISS database, safety information was available for subjects who received TQ 300mg, < 300mg and > 300mg. Patients received TQ with or without CQ in these studies. Fatigue was the most commonly reported AE regardless of dose or duration of TQ therapy, (Table 62.

In the TQ 300mg treatment group, 22/810 (2.7%) patients experienced decreases in Hgb levels. Decreases in Hgb were reported in 11/2897 (0.4%) subjects who received doses of TQ > 300mg; this population included healthy subjects who received TQ with and without CQ, military personnel who took TQ 200mg weekly for malaria prophylaxis for up to six months, as well as patients who received TQ + CQ for treatment of *P. vivax* malaria.

In the TQ <300mg group, 5(1.3%) patients experienced decreases in Hgb levels. Decreases in Hgb levels was reported in 4/794 (0.5%) in the placebo/ CQ-group. Anemia (not otherwise specified), hemolytic anemia and hemolysis was reported in 18/2897 (0.6%) subjects receiving doses of TQ >300mg, 1/810 (0.1%) subjects in the TQ 300mg group, and 9/794 (1.2%) subjects in the placebo/ CQ group. Data for hematocrit decreases were not available for the TQ 300mg and > 300mg dose groups.

Increases in serum bilirubin / hyperbilirubinemia was reported in 12/2897 (0.4%) of subjects in the TQ > 300mg group, 2/810 (0.2%) in the TQ 300mg group, and 9/794 (1.1%) in the CQ-treated subjects. Measurements of indirect bilirubin, an indicator of hemolysis was not available for all patients. Urine bilirubin test results were available in some studies. The cut-off values to define clinically significant decreases in Hgb levels were slightly different among studies.

Table 62. Integrated Safety Population: Hematological SMQ Adverse Events by Treatment Arm

		Pooled Treatment Groups							
		>300mg TQ		Placebo or CQ*		300mg TQ		<300mg TQ	
		N=2897		N=794		N=810		N=392	
System Organ Class	**Preferred Term**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
General disorders and administration site conditions	Fatigue	38	1.3%	17	2.1%	5	0.6%	3	0.8%
Investigations	Hemoglobin decreased	11	0.4%	4	0.5%	22	2.7%	5	1.3%
	Blood bilirubin increased	6	0.2%	3	0.4%	1	0.1%	.	.
	Hematocrit decreased	.	.	2	0.3%	.	.	1	0.3%
	Hematocrit increased	.	.	1	0.1%	.	.	.	.
	Reticulocyte count increased	1	0.0%	.	.	.	.	.	.
Blood and lymphatic system disorders	Anemia	14	0.5%	7	0.9%	1	0.1%	1	0.3%
	Hemolytic anemia	3	0.1%	.	.	.	.	.	.
	Microcytic anemia	.	.	2	0.3%	.	.	.	.
	Hemolysis	1	0.0%	.	.	.	.	.	.
	Reticulocytosis	.	.	.	.	.	.	1	0.3%
Hepatobiliary disorders	Hyperbilirubinemia	6	0.2%	6	0.8%	1	0.1%	1	0.3%
Respiratory, thoracic and mediastinal disorders	Dyspnea	2	0.1%	.	.	2	0.2%	.	.
	Tachypnea	.	.	.	.	1	0.1%	.	.
Renal and urinary disorders	Hemoglobinuria	1	0.0%	.	.	.	.	.	.
Vascular disorders	Pallor	.	.	.	.	1	0.1%	.	.

This analysis includes data from 19 studies, TAF006, TAF030, TAF033, TAF 057, TAF058, TAF112582, TAF047, TAF040, TAF106491, TAF003, 201807, 200951, TAF015, TAF045, TAF022, TAF110027. *The placebo group includes healthy volunteers who received a placebo and *P. vivax* patients treated with CQ alone in studies TAF112582 and TAF047. Source: NDA 210795, ADSL and ADAE datasets in ISS, JUMP Clinical v. 12.2.0

Patients with decreases in Hgb > 3g/dL- a protocol specified SAE

Characteristics of the patients who experienced decreases in Hgb levels > 3g/dL in TAF112582, part 2 are summarized in Table 63. Fourteen (5.4%) subjects in the TQ 300mg+CQ group, 2 (1.1%) in the PQ+CQ group and 2 (1.1%) patients in the CQ/placebo controlled trials experienced decreases in Hgb > 3g/dL. The maximum Hgb decrease from baseline was 4.2g/dL (from baseline 15.6g/dL) in the TQ 300mg+CQ group, (Table 64). The largest proportion of discontinuations (n=11, 4%) from study drugs were due to decreases in Hgb levels. It should be noted that patients had received a single-dose TQ 300mg before treatment was discontinued or interrupted. Patients were asymptomatic. The decreases in Hgb levels were diagnosed

between Day 3 up to Day 16 of the trial.

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***Clinical Reviewer's Comment**: All patients who experienced decreases in Hgb levels were asymptomatic and recovered without a blood transfusion. These SAEs do not preclude the use of TQ+CQ for treatment of P. vivax malaria from a clinical perspective. Monitoring for clinical signs and symptoms of hemolysis and hemolytic anemia is advisable especially for patients who are anemic at baseline.*

Table 63. TAF112582 part 2: Subjects with decreases in hemoglobin > 3g/dL or ≥ 30% from baseline

Unique Subject Identifier USUJID	*study Site #*	*AGE*	*SEX*	*Race*	*Country*	*Actual Treatment*	*Study Day of Start of AE*	*Study Day of End of AE*	*Hgb decrease ≥3g/dL from baseline*	*Duration of AE*	*Action Taken with Study Drugs*	*Outcome of Adverse Event*	*Max. Grade or Intensity*	*Time (days) from First Dose to Start*	*Protocol specified SAE*
	87400	18	F	MULTI	Brazil	PQ+CQ	11	13	Y	3 DAYS	dose not changed	RECOVERED	1	11	Y
	87400	38	F	MULTI	Brazil	TQ+CQ	8	26	Y	19 DAYS	dose not changed	RECOVERED	2	8	Y
	87400	53	M	MULTI	Brazil	TQ+CQ	5	8	Y	4 DAYS	drug withdraw	RECOVERED	2	5	Y
	87400	25	M	MULTI	Brazil	TQ+CQ	10	13	Y	4 DAYS	drug withdrawn	RECOVERED	2	10	Y
	87400	43	F	MULTI	Brazil	TQ+CQ	11	40	Y	30 DAYS	drug withdraw	RECOVERED	2	11	Y
	87400	53	M	MULTI	Brazil	TQ+CQ	12	20	Y	9 DAYS	drug withdraw	RECOVERED	2	12	Y
	87400	45	M	MULTI	Brazil	TQ+CQ	7	26	Y	20 DAYS	drug withdraw	RECOVERED	2	7	Y
	203376	26	M	WHITE	Brazil	TQ+CQ	16	24	Y	9 DAYS	not applicable	RECOVERED	1	16	Y
	100625	29	M	ASIAN	Philippines	TQ+CQ	8	14	Y	7 DAYS	drug withdraw	RECOVERED	1	8	Y
	207022	23	M	BLACK OR AFRI-AMER	Ethiopia	CQ only	8	11	Y	4 DAYS	drug withdraw	RECOVERED	1	8	Y
	207022	37	M	BLACK OR AFRI -AMER	Ethiopia	TQ+CQ	16	36	Y	21 DAYS	not applicable	RECOVERED	1	16	Y
	87400	45	M	MULTI	Brazil	TQ+CQ	3	6	Y	4 DAYS	drug withdraw	RECOVERED	2	3	Y
	87400	47	M	MULTI	Brazil	CQ only	3	5	Y	3 DAYS	drug withdraw	RECOVERED	2	3	Y
(b) (6)	87400	51	M	MULTI	Brazil	TQ+CQ	8	12	Y	5 DAYS	drug	RECOVERED	1	8	Y

Unique Subject Identifier USUJID	*study Site #*	*AGE*	*SEX*	*Race*	*Country*	*Actual Treatment*	*Study Day of Start of AE*	*Study Day of End of AE*	*Hgb decrease ≥3g/dL from baseline*	*Duration of AE*	*Action Taken with Study Drugs*	*Outcome of Adverse Event*	*Max. Grade or Intensity*	*Time (days) from First Dose to Start*	*Protocol specified SAE*
											withdraw				
(b) (6)	87400	19	M	MULTI	Brazil	TQ+CQ	3	5	Y	3 DAYS	drug withdraw	RECOVERED	1	3	Y
	87400	54	F	MULTI	Brazil	PQ+CQ	13	20	Y	8 DAYS	not applicable	RECOVERED	1	13	Y
	87400	21	F	MULTI	Brazil	TQ+CQ	13	19	Y	7 DAYS	drug withdraw	RECOVERED	1	13	Y
	87400	30	F	MULTIPL	Brazil	TQ+CQ	3	5	Y	3 DAYS	drug withdraw	RECOVERED	2	3	Y

Source: NDA 210795, study TAF112582 part 2, ADSL and ADAE datasets - Analysis in MAED

Reticulocytosis

Reticulocytosis is a key finding indicating hemolysis when a decrease in Hgb is not explained by hemorrhage or a nutritional deficiency. Other manifestations of hemolysis include the presence of schistocytes on peripheral blood smear, increases in lactate dehydrogenase and indirect bilirubin, and decreases in haptoglobin levels. In the two placebo (CQ)-controlled trials, Hgb levels, reticulocyte counts, total bilirubin, and urine bilirubin test results were available for most of the patients and are summarized in Table 64. The nadir in Hgb levels occurred between study Day 3 to Day 15 and mean Hgb levels increased toward normal baseline values between Day 5 to Day 29.

In TAF112582 Part 1, 6 (2%) subjects experienced a decline in Hgb >2.5 g/dL or ≥25% drop from baseline, a predefined SAE. i.e., three in the TQ300mg+CQ group, two in the CQ only group, and one in the TQ 600mg+CQ group. Patients who received TQ 300mg + CQ are summarized in Table 64. Subject # (b) (6) in the TQ 300mg + CQ was the only subject who did not fulfill the SAE criteria as the nadir of the Hgb decline was at Day 22 and outside the pre-defined 15-day window post treatment. Blood samples from each subject were sequenced for G6PD deficiency and all were found to be negative for mutations. One patient, # (b) (6) who was treated with TQ 300mg+CQ experienced a decrease in Hgb > 3g/dL from 11.2 g/dL at baseline to 7.7g/dL on Day 3 and remained on study drugs. The subject had pallor and received treatment with iron and folate supplements. Urine bilirubin dipstick was positive, indicating direct bilirubin elevations and suggesting liver injury.

In TAF112582 Part 2, decreases in Hgb levels >3.0 g/dL or ≥30% drop from baseline accompanied by increases in reticulocyte counts occurred in 7 (2.6%) patients in the TQ+CQ group, zero patients in the CQ group and in 2 (1.5%) subjects in the PQ+CQ group. The maximum drop in Hgb was 4.2g/dL and was associated with increases in reticulocyte counts (subject (b) (6), Table 64). There were no significant increases in reticulocytes in the other seven patients treated with TQ 300mg+CQ and two patients in the CQ group (Table 64). Some patients had elevated total bilirubin levels at baseline which was probably associated with *P. vivax* malaria. Total bilirubin levels declined on treatment. Urine dipstick was positive for bilirubin in one subject and suggesting liver injury (see section on hepatic adverse events).

Table 64. TAF 112582 Part 1 and 2: Hematological Serious Adverse Events – Hgb decreased

Site / Subject no.	*Gender/ Age*	*Hgb g/dL baseline (Day 1)*	*Hgb g/dL nadir/ Day #*	*Hgb g/dL at end of event/ Day#*	*Reticulocyte Ct. % baseline / max. post-base*	*Total bilirubin mg/dL baseline /max. post-base*	*Urine bilirubin*
TAF112582 part 2.							
TQ 300mg+CQ, N=14							
(b) (6)	F / 38y	14.1	10.8 (day 8)	11.4 (day 11)	1.5/ 5.2	1.2/0.64	Neg
	M / 54y	14.8	11.6 (day 5)	13.4 (day 8)	1.4/1.7	1.97/ 0.93	Neg
	M / 24y	14.7	11.5 (day 8)	12.5 (day 13)	0.9/1.8	2.2/0.80	Neg

Site / Subject no.	*Gender/ Age*	*Hgb g/dL baseline (Day 1)*	*Hgb g/dL nadir/ Day #*	*Hgb g/dL at end of event/ Day#*	*Reticulocyte Ct. % baseline / max. post-base*	*Total bilirubin mg/dL baseline /max. post-base*	*Urine bilirubin*
(b) (6)	F / 43y	15.5	12.1 (day 11)	11.46 (day 22)	1.6/ 3.4	0.85 /0.84	Neg
	M / 53y	15.6	11.4 (day 11)	12.8 (day 22)	2.2/3.5	2.19/1.73	Neg
	M / 45y	17.0	13.2 (day 3)	16.7 (day 5)	1.2/1.4	3.57/1.28	Neg
	M / 51y	15.3	12.3 (day 8)	15.2 (day 11)	2.6/2.1	0.6/0.38	Neg
	M / 19y	15.1	12.1 (day 3)	12.6 (day 5)	0.9/1.8	2.46/1.64	Pos → Neg
	F / 21y	14.0	11.1 (day 15)	11.3 (day 22)	2.1/3.2	0.73/1.01	Neg
	F / 30y	13.1	10.0 (day 3)	11 (day 5)	1.1/3.6	2.39/1.36	Neg
	M / 45y	14.5	10.9 (day 8)	12.0 (day 29)	1.0/5.3	1.03/1.02	ND
	M / 29y	18.1	15.0 (day 5)	15.3 (day 11)	1.1/1.3	1.01/0.96	ND
	M / 26y	15.2	12.1 (day 15)	12.6 (day 29)	0.9/1.1	0.9/1.06	Neg
	M / 37y	12.0	8.8 (day 15)	9.3 (day 22)	1.4/7.3	2.3/1.46	Neg
PQ+CQ, N=3							
(b) (6)	F / 54y	14.6	11.1 (day 15)	13.1 (day 22)	1.5/3.0	1.93/1.37	Neg
	F / 18y	13.9	10.7 (day 11)	11.1 (day 15)	1.7/6.1	1.35/0.68	Neg
	F/ 56y	12.4	9.5	10.1	NR	NR	NR
CQ only, N=3							
(b) (6)	M / 23y	13.9	10.8 (day 8)	12.2 (day 11)	1.7/2.1	2.23/2.49	Neg
	M/ 47y	16.2	12.5 (Day 3)	14.1 (day 5)	1.0/1.0	0.6/0.94	ND
	M/ 34y	15.9	12.9 (day 6)	13.4 (day 20)	NR	NR	NR
TAF 112582 Part 1.							
TQ 300mg + CQ, N=2							
(b) (6)	M / 52y	11.2	7.7 Anemia, grade 2 (day 2)	NR day 16	NR	NR	Pos
	M / 47y	*16.5*	*13.5 (day 16)*	*15.3 (day 26)*	*NR*	*NR*	*NR*
Normal ranges approx. for reference	-	*13-16 g/dL*	*13-16 g/dL*	*13-16 g/dL*	*0.56-2.72 %*	*0.01-1.3 mg/dL*	*Neg*

ND: not done; NR; not reported;
Normal ranges: *The investigator reported that different machines were used to measure hemoglobin on Day 1 and Day 3, compared to Day 5 and after and that the two machines have different normal ranges.
† 1403 received TQ on Day 1.
§Patient (b) (6) was dehydrated with high urea level at screening. He had a high CPK (1085 IU/L) level at screening which resolved to 145 U/L by Day 3 (no intervention reported).
‡At Day 29, Hgb=11g/dL and at a subsequent unscheduled visit, Hgb=13g/dL.
¶Patient (b) (6): Blood drawn 1 day post treatment showed a Hgb= 7.7 g/dL. Pt. was pale and received iron, B12, and folate. Study drugs were continued. Anemia resolved at Day 16 post treatment.
¶¶Patient # (b) (6) had a protocol violation – on Day 2, met stopping criteria for a decrease in Hgb >2.5 g/dL from baseline but PQ was continued. Iron supplement was prescribed. PQ was continued for 14 days. Patient was asymptomatic.
(b) (6) The study report states that there was no clinical or laboratory evidence of hemolysis.
Source: NDA 210795, TAF112582 part 2, CSR, section 13.0, Case narratives.

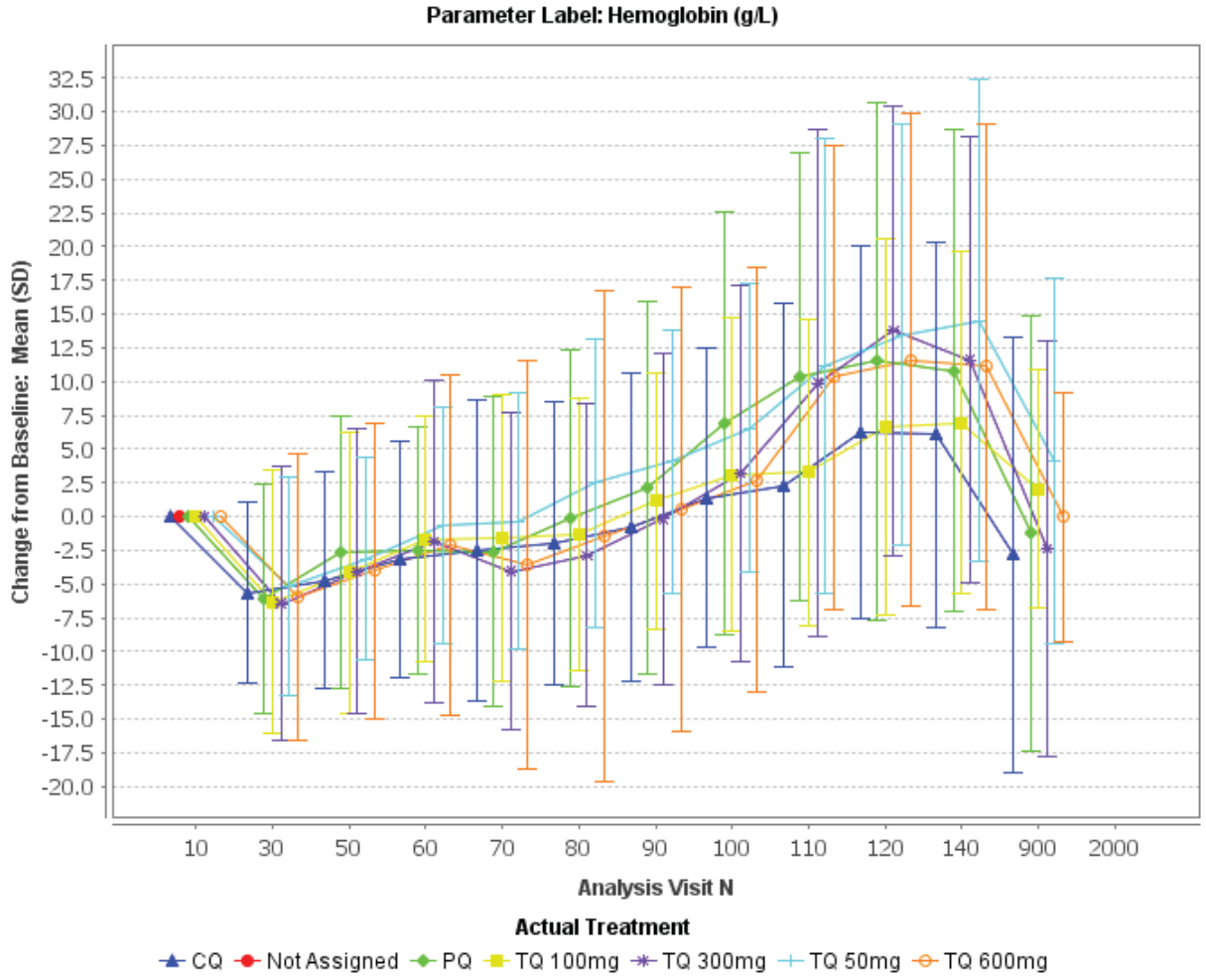
Risk of decreases in Hgb with the TQ+CQ group

In pooled TQ300mg treatment groups in TAF112582 part 1& 2, an analysis of risk using the exact meta-analysis method did not show a significantly increased risk of hemolysis in the TQ +CQ treatment group when compared to CQ alone. The TQ 300mg+CQ groups had a numerical higher incidence of Hgb decrease versus CQ. In TAF112582 Part 2, the difference in risk of hemoglobin decrease between TQ+CQ and CQ groups was also not statistically significant. Overall, there was no statistically significant increased risk of hemolysis with the TQ+CQ group.

Change in hemoglobin levels from baseline by study visit

In study TAF112582, part 1 (n=329), all treatment groups showed a post-baseline decline in mean Hgb (g/dL) at around Day 3 (visit #30), Figure 6. All treatment groups showed recovery of Hgb levels to baseline levels or to higher Hgb levels post treatment. The subjects in the CQ and the TQ+CQ treatment group recovered Hgb levels to baseline levels around Day 29 (visit #100).

Figure 6. TAF112582, Part 1: Change in mean hemoglobin g/L from baseline by study visit - Safety population



Visits N/study day: Day of study Visit 10: Day 1, Visit 30: Day 3, Visit 40: day 4, Visit 50: Day 5, Visit 60: Day 8, Visit 70: Day 11, Visit 80: Day 15, Visit 90: Day 22, Visit 100: Day 29, Visit 110: Day 60, Visit 120: day 90, Visit 130: Day 120,Visit 140: Day 180, Visit 160: EOS, Visit: 900 unscheduled.
Visit 900: include only patients who had unscheduled visits during the study.
Source: NDA 210795, Study TAF112582 part 1, ADLAB datasets.

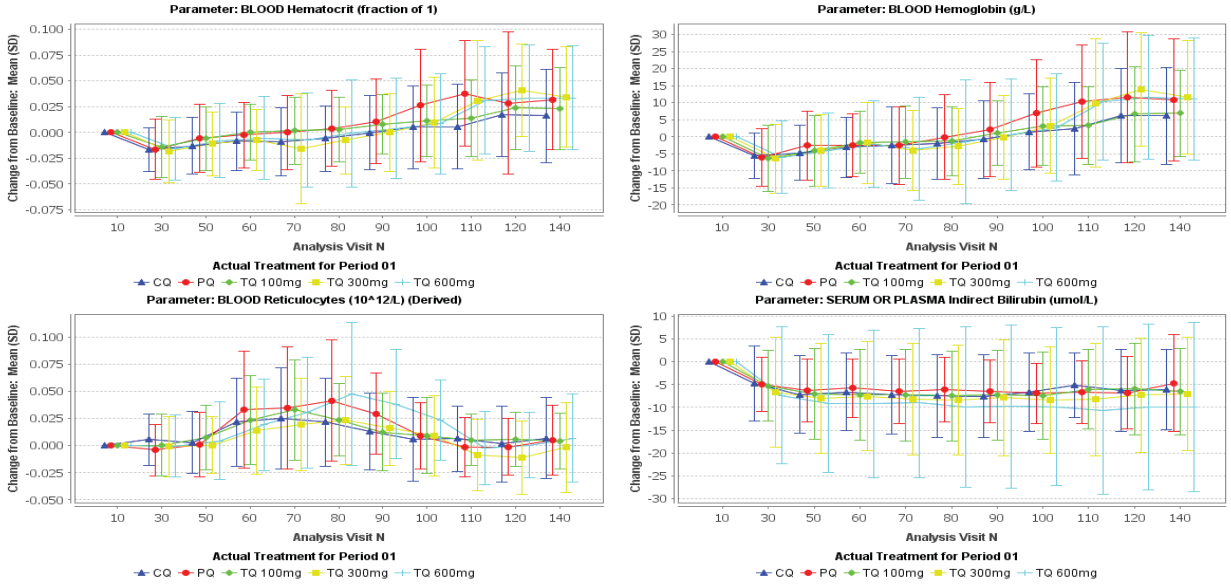
Reticulocyte Counts

Decreases in Hgb were associated with increases in reticulocyte counts 10^{12}/L over time up to Day 15 across all treatment groups. Some patients had elevated bilirubin levels at baseline probably associated with *P. vivax* malaria.

The largest mean increase in reticulocyte counts for TQ-treated patients was observed in the TQ 600mg + CQ group, i.e. mean increase of 2.2% on Day 15, from a baseline mean of 1.1%. Subjects in the TQ 300mg +CQ treatment group showed an increase of 2% in mean reticulocyte counts on Day 15 compared to a mean increase of 1.5% and 1.6% in the TQ 100mg and TQ 50mg groups, respectively. For PQ, a peak in the mean reticulocyte count of 2.2% at Day 15 was observed. In the CQ group, a peak mean value of 1.7% was seen at Day 11. All subjects were at

or below mean baseline reticulocytes by Day 60 (visit #110). Indirect bilirubin (µmol/L) declined on treatment, Figure 7.

Figure 7. TAF112582, Part 1: Changes in Mean (SD) Hemoglobin, Hematocrit, Reticulocytes, and Bilirubin by Study Visit - Safety Population



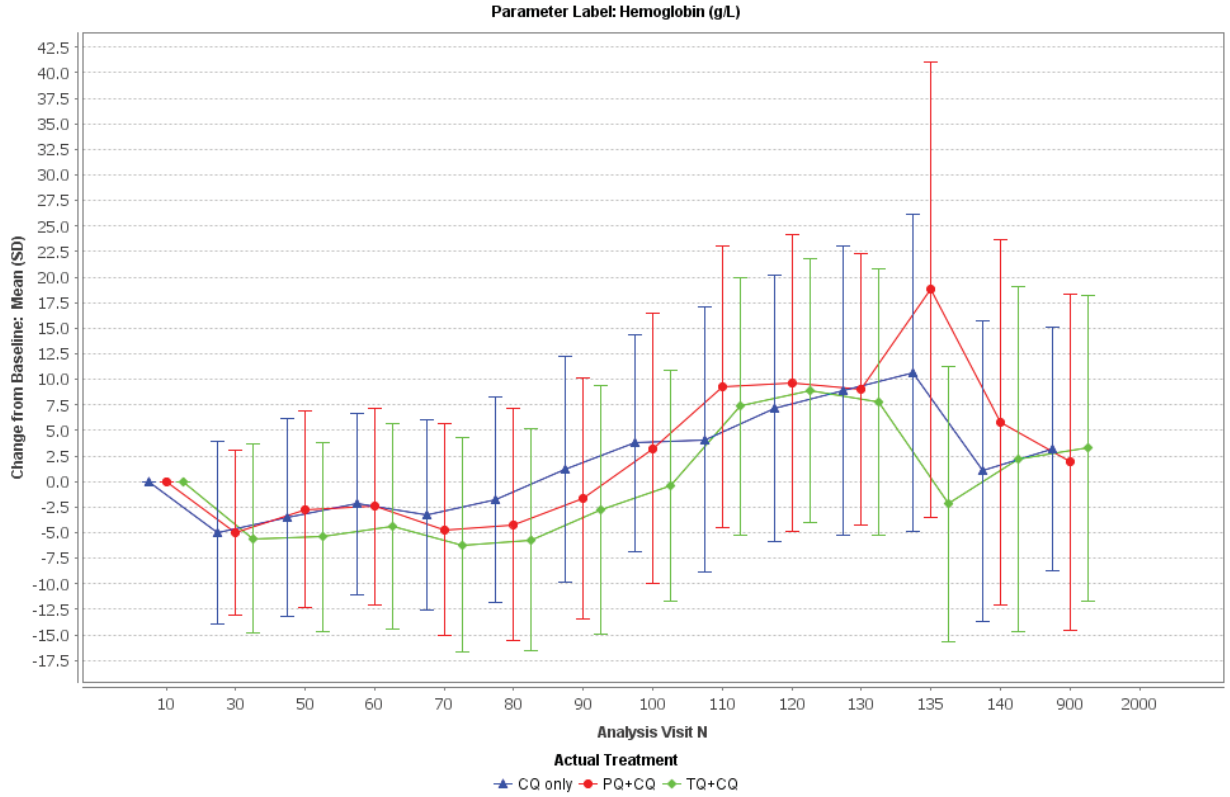
Study 582 part 1.
TQ:Tafenoquine; PQ: Primaquine: CQ:Chloroquine.

TQ 50mg+CQ is not shown.
SD: standard deviation. Visits N/Study day: Day of Visit 10: Day 1, Visit 30: Day 3, Visit 40: Day 4, Visit 50: Day 5, Visit 60: Day 8, Visit 70: Day 11, Visit 80: Day 15, Visit 90: Day 22, Visit 100: Day 29, Visit 110: Day 60, Visit 120: Day 90, Visit 130: Day 120,Visit 140: Day 180. Source: Study 582 part 1: Laboratory dataset, JReview 12.0

Clinical Reviewer's Comment*: Decreases in Hgb levels due to hemolysis is an expected finding in patients with malaria. Overall, increases in reticulocytes counts were small. The pattern of reticulocytosis observed is consistent with recovery from vivax malaria. The laboratory data did not support significant hemolysis due to TQ however, TQ cannot be ruled out as a contributing factor to the decline in Hgb levels because the incidence of this adverse event was higher in the TQ+CQ group as compared to the CQ group,* Table 52.

In TAF112582, part 2 (n=522), the pattern of decline in mean Hgb (g/L) levels and recovery over time was similar across the TQ+CQ, PQ+CQ, and CQ only treatment groups. The subjects in CQ group recovered their baseline Hgb levels around Day 22, and subjects in the TQ+CQ and PQ+CQ returned to baseline values approximately one week later around Day 29, (Figure 8).

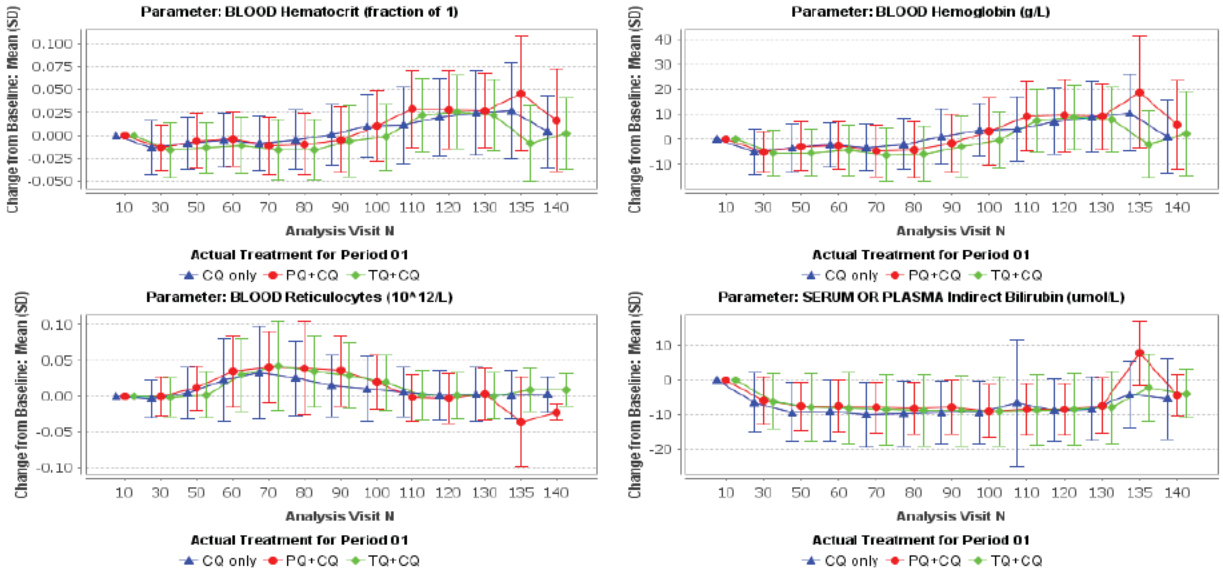
Figure 8. TAF112582, Part 2: Mean change in hemoglobin g/L from baseline by study visit - safety population.



Visits N/study day: Day of study Visit 10: Day 1, Visit 30: Day 3, Visit 50: Day 5, Visit 60: Day 8, Visit 70: Day 11, Visit 80: Day 15, Visit 90: Day 22, Visit 100: Day 29, Visit 110: Day 60, Visit 120: day 90, Visit 135: Day 150, Visit 140: Day 180, Visit 150: Withdrawal, Visit 160: EOS, Visit 900: unscheduled visit,
Visit 900: include only patients who had unscheduled visits during the study.
Source: NDA 210795, Study TAF112582 part 2, ADSL and ADLAB datasets, JReview11.0

An increase in reticulocyte counts occurred in all treatment groups from Day 8 (visit #60) to Day 22 (Visit #90), Figure 9. Reticulocyte counts returned to baseline by Day 60. The pattern of increase in reticulocyte counts parallels the decrease in Hgb levels over the study period. Some patients had elevated bilirubin levels at baseline probably associated with *P. vivax* malaria. Baseline elevations in total and indirect bilirubin returned to normal limits for most subjects by Day 3 to Day 5 on completion of the anti-malarial treatment regimens. The laboratory data did not support significant hemolysis due to TQ, Figure 9.

Figure 9. TAF112582, Part 2: Changes in Mean (SD) Hemoglobin, Hematocrit, Reticulocytes, and Bilirubin by Study Visit - Safety Population.



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

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

<u>Hemoglobin g/dL decrease from baseline by treatment arm, study Day 1 through Day 29</u>

In study TAF112582 part 1 (n=329), during the first month of the trial, the frequency of significant decreases in Hgb > 2.5g/dL was similar (2 to 4%) across treatment groups, TQ 300mg+CQ, PQ+CQ, and CQ treatment groups through Day 29, Table 65. The frequency of smaller decreases in Hgb >1.5 to ≤ 2.5g/dL from baseline were similar across treatment groups i.e., 30% in the TQ300mg +CQ and PQ+CQ groups.

Hgb decreases of >2.5 g/dL (or ≥25% drop from baseline) were to be reported as SAEs if they occurred with first 15 days of treatment; six subjects (5 males and 1 female) were in this category. One subject, did not fulfill the SAE criteria as the nadir of the Hgb decline was observed at Day 22. Patients were asymptomatic and did not require medical intervention such as blood transfusion. Gene sequencing for G6PD mutations were negative in the six subjects.

Table 65. TAF112582, part 1: Hemoglobin g/dL decrease from baseline by treatment arm during first 29 days – Safety population

Hemoglobin (Hgb) decrease from baseline	CQ + TQ 50 mg, N=55	CQ + TQ 100 mg, N=57	CQ + TQ 300 mg, N=57	CQ + TQ 600 mg, N=56	CQ + PQ 15 mg daily x 14 days, N=50	CQ, N=54
>1.5 and ≤ 2.5g/dL	7(13%)	19(33%)	17(30%)	22(39%)	15(30%)	15 (28%)
> 2.5g/dL or ≥25% of baseline	0	1(2%)	2(4%)	1(2%)	1(2%)	1(2%)

Source: NDA 210795, TAF112582 part 1, ADAE and ADLAB datasets.

In TAF112582 part 2 (n=522), in the first 29 days of the trial, 14 (5%) patients treated with TQ 300mg +CQ experienced a higher frequency of decreases in Hgb > 3g /dL as compared to 3 (2%) patients PQ +CQ and 2 (4%) patients in the CQ treatment groups, Table 66. More than 80% of the patients in all treatment groups experienced Hgb decreases from 0 to ≤ 2g/dL which were not considered clinically significant.

Table 66. TAF112582, part 2: Hemoglobin g/dL decrease from baseline by treatment arm during first 29 days – Safety population

Hemoglobin (Hgb) g/dL decrease from baseline	CQ+TQ 300mg N=260	CQ+ PQ 15mg N=129	CQ N=133
> 2g/dL and ≤ 3g/dL	31 (12%)	12 (9%)	11 (8%)
> 3g/dL or ≥ 30% of baseline	14 (5%)	3 (2%)	2 (2%)

Source: NDA 210795, TAF112582 part 2, ADAE and ADLAB datasets, JReview 11.0

Hemoglobin Decreases – Toxicity Grades

In TAF112582 part 1 and Part 2, decreases in Hgb (g/dL) from baseline were generally mild to moderate (CTCAE grade 1 or 2), in severity and were similar across treatment groups, (Table 67 and Table 68).

Table 67. TAF112582, part 1: Hematology Laboratory Tests - Toxicity Grades

Test	Baseline Grade	Maximum Grade Post Baseline	CQ	PQ	TQ 100mg	TQ 300mg	TQ 600mg
Hemoglobin Hgb g/L Decrease	0	0	4(7.4%)	5 (10.0%)	7 (12.3%)	2 (3.5%)	4 (7.1%)
		1	17(31.5%)	13 (26.0%)	17 (29.8%)	17 (29.8%)	15 (26.8%)
		2	1 (1.9%)	1 (2.0%)	0	0	0
	1	0	1 (1.9%)	0	0	0	0
		1	23 (42.6%)	20 (40.0%)	25 (43.9%)	28 (49.1%)	25 (44.6%)
		2	4 (7.4%)	4 (8.0%)	5 (8.8%)	3 (5.3%)	2 (3.6%)
		3	0	0	0	1 (1.8%)	0
	2	0	0	0	0	0	1 (1.8%)
		1	0	1 (2.0%)	0	1 (1.8%)	0
		2	2 (3.7%)	3 (6.0%)	0	3 (5.3%)	3 (5.4%)
		3	0	0	1 (1.8%)	0	0
	3	2	0	1 (2.0%)	0	0	1 (1.8%)
		3	0	0	0	1 (1.8%)	1 (1.8%)
		4	0	0	0	0	1 (1.8%)

Table 68. TAF112582, part 2: Hematology Laboratory Tests - Toxicity Grades

Laboratory test result	Baseline Grade	Maximum Grade Post Baseline	TQ 300mg +CQ N=260	CQ only N= 133	PQ+CQ N=129
Hemoglobin (Hgb) g/dL Decrease	0	0	55 (21.2%)	27 (20.3%)	26 (20.2%)
		1	88 (33.8%)	44 (33.1%)	46 (35.7%)
		2	3 (1.2%)	0	0
	1	0	1 (0.4%)	1 (0.8%)	1 (0.8%)
		1	91 (35.0%)	51 (38.3%)	52 (40.3%)
		2	18 (6.9%)	8 (6.0%)	2 (1.6%)
	2	1	0	1 (0.8%)	0

Laboratory test result	Baseline Grade	Maximum Grade Post Baseline	TQ 300mg +CQ N=260	CQ only N= 133	PQ+CQ N=129
		2	2 (0.8%)	1 (0.8%)	1 (0.8%)
		3	1 (0.4%)	0	0
		4	0	0	1 (0.8%)

Source: NDA 210795, TAF112582 part 2, ADSL and ADLAB datasets, JReview 11.0

G6PD Status

There were no patients with phenotypic G6PD in TAF112582 part 1 and 2. Due to the risk of hemolytic anemia, patients were excluded from the trial if they had a G6PD enzyme activity level <70% of the site median value (8.2 IU/gHb) for G6PD normal individuals. Regional G6PD values (70% of median) were similar across the study regions i.e., 5.8 IU/gHb in South America, 5.6 IU/gHb in S.E. Asia, 5.7 IU/gHb in Africa). In this trial, the minimum G6PD enzyme level of any subject was 5.4 IU/gHb.

However, genetic analysis for a G6PD genetic mutation was positive in two female subjects with a *Viangchan* G6PD mutation classified as WHO Class 2; both patients (one in the TQ+CQ group and one in the PQ+CQ group) experienced decreases in Hgb (~ 2.5g/dL) and increases reticulocyte counts comparable with the changes from baseline observed in subjects with normal G6PD. Neither subject required medical intervention such as blood transfusion. Concomitant increases in reticulocytes and indirect bilirubin levels occurred in the same timeframe as the Hgb decline. MetHb% increased from 0.5% at baseline to maximum of 3% in both patients.

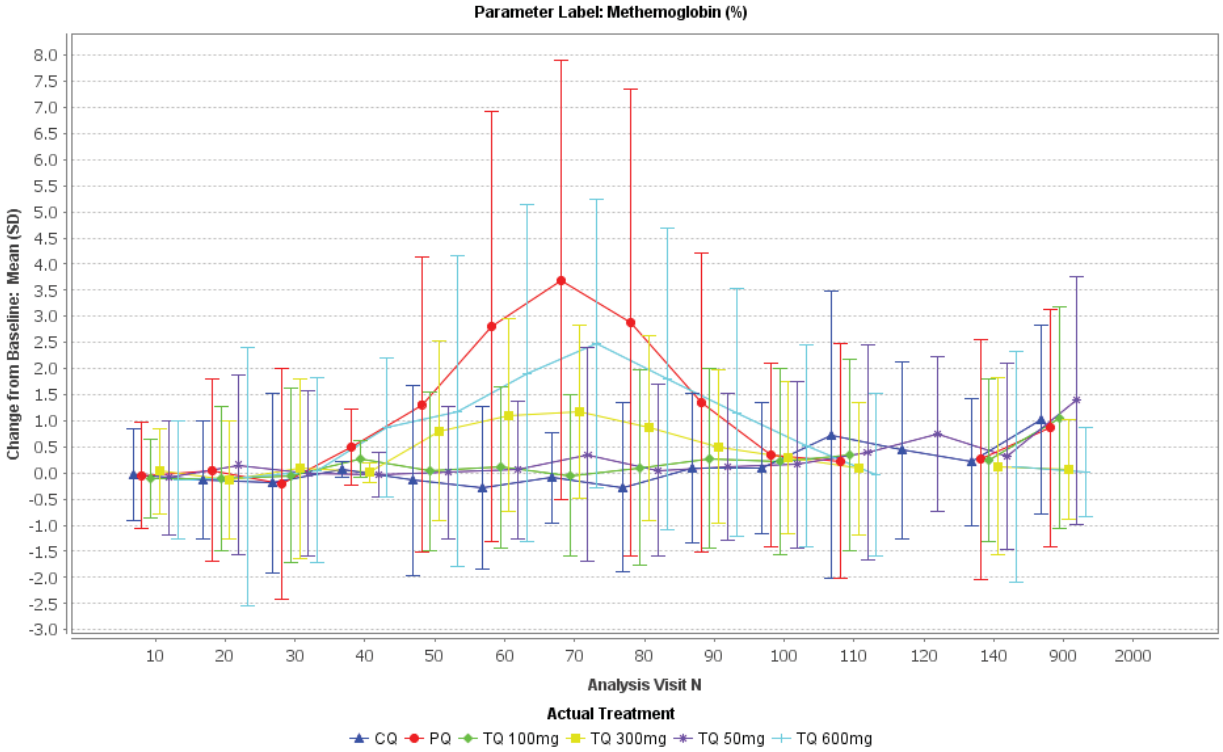
Clinical Reviewer's Comment: *Drug-induced mild hemolysis and increase in methemoglobin cannot be excluded in these two subjects with G6PD genetic mutations.*

Methemoglobinemia

There were no SAEs related to methemoglobinemia in the TQ 300mg+CQ arms in the placebo-controlled trials.

One case of methemoglobinemia was reported in PQ + CQ arm in TAF112582 part 1. In TAF112582, part 1 (N=329), the largest increases in MetHb % were also observed in the PQ + CQ group as compared to the other treatment groups. A dose-related increase in MetHb % across the TQ treatment groups (50mg to 600mg) was observed with maximum increases in MetHb % in the TQ 600mg+CQ occurring at Day 11 (visit# 70),Figure 12. No similar increases in MetHb % were observed in the CQ arm. Increases in MetHb % resolved by Day 60 (visit# 110). No subject had a MetHb value >13% and the maximum value of MetHb% observed in the TQ+CQ groups was 8% (normal < 3%).

Figure 10. TAF112582, Part 1: Change in mean methemoglobin % from baseline by study visit - Safety population

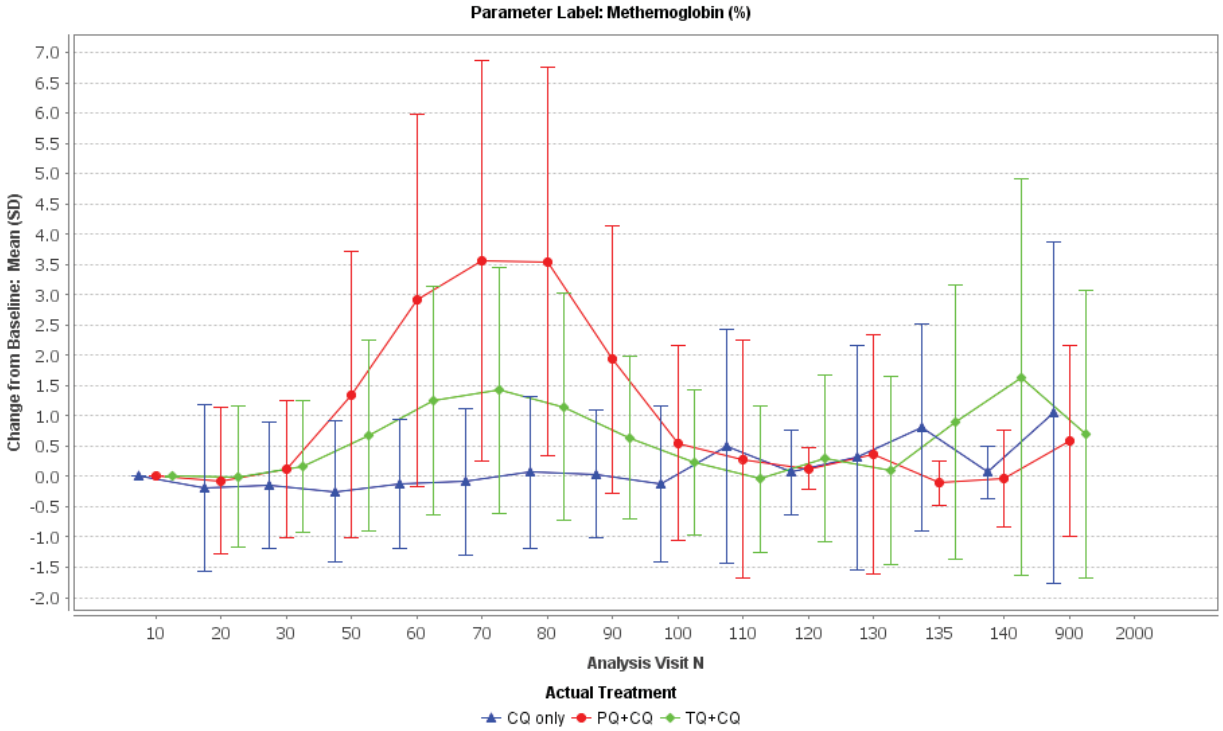


Visits #: Day of study. Visit 10: Day 1; Visit 30: Day 3; Visit 50: Day 5; Visit 60: Day 8; Visit 70: Day 11; Visit 80: Day 15;Visit 90: Day 22;Visit 100: Day 29;Visit 110: Day 60;Visit 120: day 90; Visit 130: Day 120; Visit 135: day 150;Visit 140: Day 180; Visit 150 Withdrawal; Visit 160:EOS; Visit 811 initial LE visit; Visit 3000: cardiovascular event; Visit: 900: unscheduled visit (included only patients who had unscheduled visits during the study).
Source: NDA 210795, Study TAF112582 part 1, ADLAB datasets.

In the TAF112582 part 2 (n=522), increases in methemoglobin (MetHb%) levels from baseline were more frequent in the PQ+CQ group, 11(9%) compared to the other two treatment groups, TQ+CQ 5(2%) and CQ 4(3%). The largest mean increase in MetHb% from baseline was observed in the PQ+CQ treatment group at Day 11 (Visit #70). The largest mean increase in MetHb% was 1.6% in the TQ 300mg + CQ group as compared to 3.6% in the PQ+CQ group and 1.0% in the CQ group, Figure 11. A higher proportion of subjects in the PQ+CQ group had a methemoglobin of >10% compared with the other treatment groups.

No subject had a MetHb% >13% (normal <3%) during the trial. Patients were asymptomatic. There were no clinically important differences in MetHb% observed between male and female patients in any treatment group.

Figure 11. TAF112582, Part 2: Change in mean methemoglobin % from baseline by study visit - Safety population



Visits #: Day of study. Visit 10: Day 1; Visit 30: Day 3; Visit 50: Day 5; Visit 60: Day 8; Visit 70: Day 11; Visit 80: Day 15;Visit 90: Day 22;Visit 100: Day 29;Visit 110: Day 60; Visit 120: Day 90; Visit 130: Day 120; Visit 135: Day 150;Visit 140: Day 180; Visit 150 Withdrawal; Visit 160:EOS; Visit 811 initial LE visit; Visit 3000: cardiovascular event; Visit: 900: unscheduled visit.
Visit 900: include only patients who had unscheduled visits during the study.
Note: PQ was administered to participants with P. vivax recurrences and PQ is known to cause methemoglobinemia.
Source: NDA 210795, Study TAF112582 part 2, ADSL and ADLAB datasets.

***Clinical Reviewer's Comment**: Methemoglobinemia is a known adverse reaction associated with the 8-aminoquinoline, PQ and was an expected finding with TQ. Methemoglobin levels are approximately 1 to 3% of the total hemoglobin in normal individuals. Cyanosis is usually detected when the absolute concentration of MetHb exceeds 1.5 g/dL, equivalent to 8 to 12% MetHb at normal Hgb concentrations. Acquired methemoglobinemia may become symptomatic when MetHb comprises more than 10 percent of total hemoglobin.[24] The elevations were probably transient as none of the patients had significant signs and symptoms of methemoglobinemia at the reported MetHb% levels.*

[24] Prchal, J.T. (2016). Clinical features, diagnosis, and treatment of methemoglobinemia**.** In S.L. Schrier, D.H. Mahoney, M.M. Burns (Eds.), *UpToDate.* Retrieved July 14, 2018, from https://www.uptodate.com/contents/clinical-features-diagnosis-and-treatment-of-methemoglobinemia

Cardiac Treatment Emergent Adverse Events - Prolongation of the QT interval

In TAF112582 part 1 (n=329), QT interval prolongation was reported in 18 subjects (Table 69). Three patients met QTc criteria for withdrawal from study drugs due to QTcF > 60 ms increase from baseline; one patient in the TQ 50mg+CQ group, one patient in the PQ+CQ group, and one subject in the CQ group. Treatment was continued in the other patients who experienced QTcF interval prolongation.

Table 69. TAF112582 part 1: QTc Prolongation – Safety Population

Adverse Event	TQ50mg +CQ N=55	TQ100mg +CQ N=57	TQ300mg +CQ N=57	TQ600mg +CQ N=56	PQ+CQ N=50	CQ N=54
QTcF interval Prolongation	3 (5.5%)	2 (3.5%)	3(5.3%)	1(1.8%)	5(10%)	4(7.4%)

No differences were seen in QTcF interval changes between the CQ and TQ (50, 100, 300, 600mg) treatment groups with all groups showing the same pattern of prolongation as CQ alone, in both the frequency and magnitude of changes, (Table 70). QT interval prolongation in the TQ+CQ groups was not related to increasing TQ doses and were generally Grade 1 and 2 in severity. No patient experienced a QTcF prolongation > 500 ms at any time point.

Table 70. TAF112582, part 1: Maximum Post-Baseline QTcF through 72 Hours by Category - Safety Population

QTcF values (ms)	TQ 50mg + CQ	TQ 100mg + CQ	TQ 300mg + CQ	TQ 600mg + CQ	PQ 15mg	CQ
N (%)	55(100)	57(100)	57(100)	56(100)	50(100)	54(100)
≤450	37 (69)	101 (77)	97 (75)	38 (68)	29 (58)	34(63)
>450 ≤480	15 (25)	24 (18)	30 (23)	17 (30)	20(40)	16(30)
>480 ≤500	3 (6)	4 (3)	2 (2)	1(2)	1(2)	4(7)
N	55	57	57	56	50	54
Increase < 60	47 (85)	52 (92)	50 (90)	52(93)	44(88)	48(89)
Increase ≥ 60 [and ≤480]	7 (13)	3 (3)	7 (9)	4 (7)	5(10)	6(11)
Increase ≥ 60 [and > 480]	1(2)	2 (5)	0 (<1)	0	1(2)	0

Source: NDA 210795, TAF112582 part 1: Adapted from table submitted by the Applicant on 5/8/2018 in response to an information request.

In TAF112582 Part 2 (n=522), there were no patients with clinically significant abnormal ECG findings in the TQ 300mg + CQ treatment group. Three subjects in the CQ alone treatment group met protocol-specified criteria for study medication discontinuation due to changes in QTcF consistent with the known effects of CQ on QT interval, Table 71. The maximum postbaseline change was selected based on the largest increases from baseline. The maximum mean change from baseline in QTcF interval was 36.5ms in a patient in the TQ+CQ group through 72 hours after the start of treatment. QTcF interval was 422.06 ms at screening. CQ was administered on Day 1. The QTcF interval was 500.39 ms (mean) at 12 hours post dosing

with CQ which fulfilled the protocol defined criteria for discontinuation of study medications. The patient had received blinded TQ/TQ placebo on Day 2 just before study drugs were discontinued. The patient was asymptomatic patients remained the study for follow-up assessments. The event resolved by D3. The investigator attributed the event to CQ.

Table 71. TAF112582, part 2: Maximum Post-Baseline QTcF through 72 Hours by Category - Safety Population

QTcF values (ms)	TQ 300mg+CQ N=260 (100%)	CQ N=133	PQ+CQ N=129
N	254	132	129
≤450	176 (69)	101 (77)	97 (75)
>450 ≤480	63 (25)	24 (18)	30 (23)
>480 ≤500	15 (6)	4 (3)	2 (2)
>500	0	3 (2)	0
N	252	131	128
Increase < 60	220 (87)	121 (92)	115 (90)
Increase ≥ 60 [and ≤480]	25 (10)	4 (3)	12 (9)
Increase ≥ 60 [and > 480]	7(3)	6 (5)	1 (<1)

Source: NDA 210795, TAF112582 Part 2, CSR, Table 40 and Table 8.27.

There was no evidence of a clinically significant additional effect on QTcF values patients treated with TQ 300mg in addition to CQ. Differences in QTcF prolongation between treatment groups were not considered to be clinically significant.

Other Electrocardiographic abnormalities in TAF112582 part 1& 2

One patient in the TQ 300mg +CQ group had ST segment elevation (grade 1) which was asymptomatic; it started on Day 2 and resolved within 20 days, (Table 72). Two patients developed first degree AV block (Grade 1) on ECG which were asymptomatic. The AV block developed on study Day 3 and resolved in 54 days in one patient (M, 29y) and started on Day 31 and resolved within 24 hours in the second patient (M, 49y). These adverse events were not considered clinically significant.

Table 72. TAF112582, part 1& 2: Cardiac Treatment Emergent Adverse Events

		Treatment Arms					
		300mg TQ sd		CQ		15mg PQ od x14d	
		N= 317		N=187		N=179	
system Organ Class	Preferred Term	Count	%	Count	%	Count	%
Investigations	Electrocardiogram ST segment elevation	1	0.3%	.	.	.	.
	Electrocardiogram repolarization abnormality	1	0.3%	.	.	.	.
Cardiac disorders	Sinus bradycardia	1	0.3%	1	0.6%	1	0.6%
	Atrioventricular block first degree	1	0.3%	.	.	.	.

sd: single dose; d: day.
Source: ISS database, JUMP Clinical 6.0.

***Clinical Reviewer's Comment**: In the clinical trials, ≤ 5% of subjects in any treatment arm had an*

increase in QTc > 60ms and an QTc interval > 480ms. In the Thorough QT study in healthy volunteers, which measured time-matched change from baseline in QTcF as the primary endpoint, there was no indication of TQ effect on QTc for single doses TQ 300 mg and 600 mg as compared with placebo. The supratherapeutic dose of TQ 1200 mg showed a maximum effect on QTc within the safety margin of 10 ms identified in the US FDA E14 guidelines to demonstrate lack of effect.

QT interval prolongation is associated with other aminoquinoline antimalarials. The PQ USPI lists QTc interval prolongation in PRECAUTIONS and recommends monitoring ECG when using PQ in patients with cardiac disease, long QT syndrome, a history of ventricular arrhythmias, uncorrected hypokalemia and/or hypomagnesemia, or bradycardia (< 50 bpm), and during concomitant administration with QT interval prolonging agents. Electrocardiographic changes such as inversion or depression of T-wave and QT interval prolongation are listed as adverse reactions in the CQ phosphate USPI.
In summary, the available results of cardiac and ECG monitoring in the placebo-controlled clinical trials which evaluated a single-dose of TQ and the Thorough QT study, TAF114582, results indicate a lack of effect of TQ on the QT interval. Importantly, the clinical trials demonstrated no additive effect to the QT prolongation observed with CQ.

Hepatic Adverse Events

No subjects discontinued study treatment or withdrew from any of the three key clinical trials due to hepatobiliary AEs. There were no Hy's Law cases. The proportion of subjects with AEs in the hepatobiliary disorders SOC was similar across the treatment groups. Four (2%) subjects had hepatic adverse events in the TQ+CQ group in the placebo-controlled trials, (Table 73). One male patient (subject # (b) (6)) had an SAE of hepatitis coded as a drug-induced liver injury which may have been due to ingestion of herbal medicines. One female patient (subject (b) (6)) had hepatitis E. Two male subjects (Subject # (b) (6) and Subject # (b) (6)) developed treatment-related elevated transaminases (Grade 1 or Grade 2 severity) on TQ+CQ which resolved without medical intervention. For each treatment group, high bilirubin levels were observed at baseline and subsequently resolved with TQ+CQ or PQ+CQ treatment as would be expected for recovery from *P. vivax* malaria.

Table 73. TAF112582 & TAF116564: Hepatobiliary Treatment Emergent Adverse Events

Preferred Term	Subject ID #	Placebo - controlled Trials: TAF112582, Part 1 & 2 N = 683			Primary Efficacy and Safety Trials: TAF112582 part 1&2 and TAF116564 N = 747	
		TQ 300mg + CQ N = 317	CQ only N = 187	PQ + CQ N = 179	TQ 300mg sd + CQ N=483	PQ 15mg od x14d + CQ N= 264
Drug-induced liver injury	(b) (6)	2(0.6%)	0	0	2 (0.4%)	0
Hepatitis		3(0.6%)	0	1(0.6%)	3(0.4%)	1 (0.4%)

	(b) (6)					
Hepatitis acute		0	0	1(0.6%)	0	1 0.4%)
Hyperbilirubinemia (grade 1 or 2)		0	0	0	1 (0.2%)	1 (0.4%)
Liver disorder		0	1(0.5%)	0	0	0

Source: NDA210795, TAF112582, TAF116564 pooled ADSL, ADAE datasets, JReview 12.0

Case narratives for subjects who experienced hepatobiliary treatment emergent adverse events in the CQ+TQ (300 mg) arm in TAF112582, part 1& 2 are summarized below.

TAF 112582 part 1
No cases.

TAF112582 Part 2
Subject # (b) (6) was a 29-year-old Southeast Asian male with *P. vivax* malaria had an elevated ALT level 80 U/L and a total bilirubin 6.0mg/dL (due to elevated direct bilirubin) and mildly elevated alkaline phosphatase at screening on Day 1. CQ was administered on Day 1 through 3 and the patient received a single dose TQ 300mg on Day 2 or 3. Hepatic enzymes and total bilirubin levels improved on anti-malarial therapy. By Day 5, ALT level had decreased to 46U/L and total bilirubin decreased to 2.9 mg/dL. Urine bilirubin was negative at screening and positive from Days 3 to 15. ALT levels began to increase between Day 8 through Day 29. On Study Day 22 (~3 weeks post treatment with CQ+TQ), his ALT was 452 U/L (>10x ULN), AST was 227 U/L (5x ULN), alkaline phosphatase was 109 U/L (normal), total bilirubin had trended down to 1.8mg/dL (2x ULN) and a urine dipstick for bilirubin was negative. ALT peaked at 553 U/L on Day 29. The subject reported taking herbal medicines (unspecified) after discharge but denied use of alcohol. Herbal medicines were stopped. No imaging of the liver was performed. Laboratory results of a liver screen showed a weakly positive CMV IgM (result 1.2, reference range <0.9), which was not felt to be clinically relevant. At an unscheduled visit on Study Day 42 (~6 weeks post treatment with CQ+TQ), the ALT had fallen to 42 U/L (0 - 41 U/L) and the remainder of the liver function tests were normal. The investigator attributed this event to the use of herbal medication by the patient and not to the investigational drugs. The liver tests returned to normal prior to Day 42 after the patient was advised to stop herbal medicines.

Visit_Day	Alk Phos	ALT	AST	Ind. Bil	Tot. Bil	Ur. Bil
DAY 1	146	80	34	1.0	6.1	NEG
DAY 3	124	49	26	0.5	4.2	+
DAY 5	141	46	27	0.5	2.9	+
DAY 8	126	130	94	0.5	2.3	+
DAY 11	128	129	56	0.5	2.2	+
DAY 15	122	326	177	0.6	2.3	+
DAY 22	109	452	227	0.6	1.8	NEG
DAY 29	90	553	179	0.4	1.1	NEG

Visit_Day	Alk Phos	ALT	AST	Ind. Bil	Tot. Bil	Ur. Bil
UNSCHEDULED	73	42	19	0.4	0.9	
DAY 60	17	22	56	0.3	0.6	NEG
High	129	41	40	0.8	1	
Low	40	0	0	0	0	
Units	U/L	U/L	U/L	mg/dL	mg/dL	

Clinical Reviewer's Comment*: The elevated ALT and direct bilirubin levels prior to treatment on Day 1 were probably associated with P. vivax malaria because ALT and total bilirubin levels decreased while on therapy with CQ+TQ. However, ALT and AST began to elevate post treatment from Day 8 through Day 29, although total bilirubin levels continued to trend toward the normal range. On Day 60, ALT, AST, and bilirubin levels were within normal range. The elevations in ALT and AST levels observed on and after Day 8 could have been associated with ingestion of unspecified herbal medicines but in the absence of additional specific information or other etiology such as underlying liver disease or viral hepatitis, the elevated hepatic enzymes due to CQ+TQ (TQ half-life of ~15 days; CQ has a half-life of ~40 days) cannot be ruled out.*

Subject No. (b) (6) was a 28-year-old Hispanic female who received TQ+CQ starting Study Day 1. Her ALT at screening was 24 U/L. On Study Day 95, (> 3 months post treatment), the subject attended for an unscheduled visit due to fever, pruritus mainly in hands and feet, and moderate headache. On Study Day 98, she was followed up: subject still had some pruritus in hands and feet, mild headache, no fever, and mild jaundice. There was mild right upper quadrant tenderness on palpation. Malaria smears were negative. Her ALT peaked at 454 U/L (>8x ULN) on Study Day 105 which satisfied the criteria for a hepatic adverse event. At Study Day 113, her ALT was still elevated but had fallen to 156 U/L. The subject was not hospitalized. An ultrasound scan of the right upper quadrant abdomen showed gallstones. A repeat pregnancy test was negative. Serology for leptospirosis, hepatitis A, B, C, CMV and EBV were negative. HCV RNA PCR was negative. ANA and LKM-1 Ab were negative. Hepatitis E IgM was positive. The diagnosis was acute hepatitis E.

Clinical Reviewer's Comment*: Hepatitis occurred more than three months posttreatment and was of viral etiology (Hepatitis E) and was not related to study drugs.*

Subject No. (b) (6) was a 22-year-old Southeast Asian male. The TQ +CQ subject received TQ starting Study Day 2. On Study Day 171, (> 5 months post treatment) he presented with an abscess in the left foot after stepping on a stick ten days earlier. He took a cocktail of drugs purchased locally and alcohol to ease the pain; he denied that these were anti-malarials.
He also developed a hyperpigmented macular rash after taking the mixture of drugs for his pain. He was admitted to hospital for incision and drainage of the abscess, oral antibacterial drugs, and analgesics. He was discharged on Study Day 177.
At presentation on Study Day 171, he was noted to have an elevated ALT of 246 (>3x ULN) with a total bilirubin of 0.3 U/L and mild tenderness in the right-upper quadrant of the abdomen. His ALT at screening was 18 U/L. This was designated a hepatic adverse event. There was no evidence of auto-immune or viral hepatitis. The investigator ascribed this to the high intake of

alcohol used for pain relief. Alcohol was stopped upon admission and the ALT returned to normal levels by Study Day 186 (the end of the event).
Clinical reviewer's comment: Hepatitis related to alcohol occurred more than five months post-treatment and was not related to study drugs.

Subject No. (b) (6) was a 43-year-old Ethiopian African male randomized to TQ+CQ. His ALT at Screening was 28.8 U/L. On Day 5, his ALT was 115.2 U/L (<5xULN) and this was coded as Grade 2 severity. By Day 8, ALT had decreased to 66.1 U/L without specific medical treatment or intervention; study medication was neither interrupted nor withdrawn. This event fulfilled the criteria for a liver adverse event. The event was not an SAE. The patient recovered without medical intervention.
Clinical reviewer's comment: The elevations in hepatic transaminases were related to TQ+CQ.

Subject No. (b) (6) was a 25-year-old Ethiopian African male randomized to TQ+CQ. His ALT at screening was 24.1 U/L. On Day 8, his ALT was 74.5 U/L (<3x ULN) and fell to 56.4 U/L on Day 15, and 28.3 U/L on Day 22. The event did not fulfill the criteria for a liver adverse event, and severity did not exceed Grade 1. Study drugs was neither interrupted nor withdrawn. The event was not an SAE. The patient recovered without medical intervention.

Clinical reviewer's comment: The mild elevations in hepatic transaminases were probably related to TQ+ CQ.

Study TAF116564
Subject (b) (6) in the TQ+CQ group experienced a recurrence of *P. vivax* malaria on Study Day 145 and Grade 2 hyperbilirubinemia on Study Day 146.

Psychiatric Adverse Events
No subjects withdrew from a study due to a neuropsychiatric adverse event.
Insomnia, anxiety, and depressed mood/depression were reported as treatment emergent adverse events in a pooled analysis of psychiatric SMQs in the TAF112582 and TAF116564 trials. Insomnia was reported in 23 patients and was the most common reported psychiatric adverse event with a similar incidence across treatment groups, 15 (3.1%) patients in the TQ 300mg+CQ group versus 8 (3.0%) patients in the PQ+CQ group, (Table 74).
Anxiety was reported in five patients, 2 (0.4%) in the TQ+CQ versus 3 (1.1%) in the PQ+CQ treatment groups. In TAF112582 part 2, anxiety was reported in two subjects within the first 5 days of treatment; one subject was administered diazepam for anxiety and insomnia and symptoms resolved within 5 days. Depressed mood/depression was reported in one (0.3%) patient in the PQ+CQ group.

Clinical reviewer's comment: There was a temporal relationship between TQ+CQ administration and the development of anxiety in two patients. The temporal association between onset of anxiety suggests a possible association with the two study drugs but the number of cases and level of detail in the narratives is insufficient to draw conclusions about causality. There were no reports of anxiety in the CQ only arm in the current trials but it is a labeled adverse reaction in

the CQ USPI. Anxiety should be included in the TQ label and based on its temporal association with TQ+CQ. In the three TQ clinical trials, the incidence of insomnia was similar at 3% across all treatment groups including the CQ only group. Insomnia should be included in the Adverse reactions section of the TQ drug label. Sleep disorders such as insomnia and abnormal dreams are associated with MQ.

Table 74. TAF112582 & TAF116564: Psychiatric Treatment Emergent Adverse Events

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

Source: NDA210795, TAF112582, TAF116564 pooled ADSL, ADAE datasets, JReview 12.0

There were no case reports of depression in the TQ 300mg +CQ treatment group. One case report of depression in the TQ 600mg +CQ group in study TAF112582 part 1 is described below.

Subject No. (b) (6) was a 42-year-old male subject enrolled in TAF112582 part 1 for the treatment of *P. vivax* malaria who received oral CQ for 3 days + a single dose TQ 600 mg. At the time of reporting relevant medical conditions were chronic weakness, depression, "irregular psychiatric medical consult", and frequent but irregular use of diazepam. Relevant concomitant medication was diazepam 10 mg.
At 88 days after the start of CQ+TQ, the subject was hospitalized for depressed mood, nausea and 'epigastralgia' (epigastric pain); however, it is not stated when his symptoms started. During hospitalization, he also presented with diarrhea. He was treated with IV hydration, ranitidine 25 mg/ml/IV, dimeticone 75 mg/ml/oral; diazepam 10 mg/oral and fluoxetine 20mg/oral. The patient had pre-existing depression but denied suicidal tendencies.
The adverse events were reported as resolved two days after admission and the patient was discharged on paracetamol, metoclopramide, and given a psychiatric referral. The investigator considered that there was no reasonable possibility that the depressed mood, nausea, epigastralgia, and diarrhea may have been caused by TQ or CQ. The applicant states that this SAE was reported after the database was frozen and, therefore, does not appear as a SAE in the study report. No additional follow up was provided on the psychiatric referral. See SAEs in Table 52.

Clinical reviewer's comment: Subject (b) (6) had a history of depression and diazepam use prior to enrollment. The investigator's assessment was that the patient's depressed mood and gastrointestinal symptoms were unlikely to be associated with TQ 600mg+ CQ as he was hospitalized at 88 days (12 weeks or approximately 5 half-lives of TQ) after completing

treatment with TQ+CQ. There is no information on when the depressive symptoms started prior to the hospitalization which confounds the assessment for this patient.

In the TQ clinical development program, psychosis was reported in two patients (one patient had history of two prior psychotic episodes and one had a recent diagnosis of schizophrenia) who received single-doses of TQ 350mg or 500mg. These two cases are confounded but an association with TQ cannot be ruled out. There was one report of depressed mood in a healthy subject who received single-dose TQ 600mg in study TAF114582 (Thorough QT study).

Clinical Reviewer's Comment: Psychiatric Adverse Events
Quinoline antimalarials are not the same regarding psychiatric adverse reactions. The 8-aminoquinoline, PQ, which was approved by the FDA in 1952 and has extensive clinical use, does not include psychiatric adverse reactions in its USPI. PQ has a half-life of ~6 hours.
Anxiety, insomnia, and depression are listed as adverse reactions in USPI for the 4-aminoquinoline, chloroquine phosphate, which has an elimination half-life of CQ of approximately one to two months (median ~ 40 days). Psychiatric adverse reactions are generally associated with the long-term use of CQ or hydroxychloroquine.
The 4-quinoline-methanol, MQ, has a boxed warning for neuropsychiatric adverse reactions which can persist after the drug is stopped. The mean elimination half-life of MQ varied between 2 and 4 weeks, with an average of about 3 weeks in healthy adults. Psychiatric symptoms ranging from anxiety, paranoia, depression, hallucinations, and psychotic behavior, and insomnia have been reported with MQ.
This reviewer agrees with the applicant's proposal to include psychiatric adverse reactions in the WARNINGS section of the TQ drug label based on the two cases of psychosis described above although they are confounded. If pharmacovigilance for TQ single-dose does not reveal a risk for psychiatric adverse reactions, the label can be updated. Caution is advised for use of TQ+CQ in patients with a history of psychiatric disorder. Until further safety information is available, administration of PQ for radical cure of P. vivax malaria (and P. ovale) appears to be a safer alternative in patients with a history of psychiatric disorder. The ongoing ophthalmology study in which healthy volunteers receive TQ 200mg weekly for one year includes some psychiatric evaluations and should provide additional data on psychiatric effects of TQ.

Neurologic Adverse Events
No subjects withdrew from a study due to a neurologic adverse event. Headache and dizziness were the most common neurologic adverse events reported across the three primary efficacy and safety trials.
In the pooled placebo (CQ)-controlled trials, the incidence of headache was higher in the CQ group (21%) than in the TQ+CQ (11%) and PQ+CQ (13%) treatment groups. Dizziness occurred at similar rates (8 to 10%) across all treatment arms in the pooled placebo (CQ)-controlled trials. The overall incidence of dizziness in TQ+CQ (12%) and PQ+CQ (11%) groups was higher in the pooled primary efficacy and safety trials as compared to the placebo-controlled trials, due to higher incidence of dizziness in Study TAF116564, Table 75.

Table 75. TAF112582 & TAF116564: Central Nervous System Treatment Emergent Adverse Events - Safety Population

	Placebo (CQ) - controlled Trials: TAF112582, Part 1 & 2, N=683			Primary Efficacy and Safety Trials: TAF112582 part 1&2 and TAF116564 N=747	
Preferred Term	**TQ + CQ N = 317**	**CQ N = 187**	**PQ + CQ N =179**	**TQ 300mg + CQ N = 483**	**PQ + CQ N = 264**
Balance disorder	-	-	-	1 (0.3%)	0
Burning sensation	0	0	1 (0.6%)	0	1 (0.4%)
Dizziness	30 (9.5%)	16 (8.6%)	14 (7.8%)	59 (12.2%)	30 (11.3%)
Dysesthesia	0	0	1 (0.6%)	0	1 (0.4%)
Headache	37 (11.7%)	39 (20.9%)	24 (13.4%)	64 (13.3%)	40 (15.2%)
Hypoesthesia	-	-	-	0	1 (0.4%)
Migraine	3 (0.9%)	1 (0.5%)	0	3 (0.6%)	1 (0.4%)
Somnolence	1 (0.3%)	0	0	1 (0.2%)	0
Syncope	2 (0.6%)	0	1 (0.6%)	2 (0.4%)	1 (0.4%)
Tremor	1 (0.3%)	0	1(0.6%)	1 (0.2%)	1 (0.4%)

Source: NDA210795, TAF112582, TAF116564 pooled ADSL, ADAE datasets, JReview 12.0

Vertigo was reported in 3 (<1%) patients in the TQ + CQ group and zero patients in the CQ group. Vertigo and vestibular disorder were reported beyond 60 days post treatment with TQ+CQ and do not appear to be associated with study drugs. There were no auditory adverse effects reported in the TQ+CQ group. See Table 76.

Table 76. TAF112582 part 1 &2 andTAF116564: Ear and Labyrinthine Disorders Treatment Emergent Adverse Events – Safety Population

		Placebo - controlled Trials: TAF112582, Part 1 & 2, N=683			Primary Efficacy and Safety Trials: TAF112582 part 1&2 and TAF116564 N=747	
System Organ Class	**Preferred Term**	**TQ 300mg +CQ N=317**	**CQ N=187**	**PQ +CQ N=179**	**TQ +CQ N=483**	**PQ+CQ N=264**
Ear and labyrinth disorders	Ear discomfort	1 (0.3%)	0	0	1(0.2%)	0
	Tinnitus	0	0	1 (0.6%)	0	1(0.4%)
	Vertigo	2 (0.6%)	0	0	3 (0.6%)	0

Clinical Reviewer's Comment:
There were no auditory adverse effects reported in the TQ+CQ group. Auditory effects associated with CQ include nerve type deafness, tinnitus, and reduced hearing reported in patients with preexisting auditory damage after prolonged use. Such adverse effects would be unlikely following a three-day course of CQ.

Neurologic and psychiatric events occurring from Day 1 through Day 29 in TAF112582 part 1&2
Neurologic and psychiatric events occurring in the first month post treatment from Day 1 through Day 29 were evaluated to investigate an association of neuropsychiatric adverse events with study drugs.

In the pooled placebo-controlled trials, more patients reported dizziness in the TQ+CQ group as compared to CQ group, i.e., 25 (7.9%) vs. 6 (3.2%) during the first 29 days of the trials. Headache occurred more frequently in the CQ treatment group, [TQ (4.4%) vs. CQ (5.9%)]. The incidence of insomnia was similar in the TQ+CQ (3.8%) and PQ+CQ group 8(4.5%) and was slightly higher than the CQ (2.7%) group. Anxiety 2(0.6%) occurred more frequently in the TQ+CQ group but the numbers of patients affected were small. During the first two weeks post treatment i.e., one half-life ($T_{1/2}$) for TQ, the incidence of dizziness was higher in the TQ+CQ group, [TQ+CQ (3.8%) vs. CQ (0.5%)]. Two patients in the TQ+CQ group developed syncope related to blood draws on Day 1 and was not associated with study drugs. See Table 77.

Table 77. TAF112582 part 1 &2: Neuropsychiatric events occurring Day 1 to ≤ Day 29 – Safety Population

		Treatment Arms					
		TQ 300mg sd + CQ		PQ 15mg od +CQ		CQ	
		N= 317		N=179		N=187	
System Organ Class	**Preferred Term**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Nervous system disorders	Dizziness	25	7.9%	9	5.0%	6	3.2%
	Headache	14	4.4%	8	4.5%	11	5.9%
	Syncope	2	0.6%	.	.	.	.
	Tremor	1	0.3%	1	0.6%	.	.
	Dysesthesia	.	.	1	0.6%	.	.
	Migraine	.	.	.	.	1	0.5%
	Somnolence	1	0.3%	.	.	.	.
Psychiatric	Insomnia	12	3.8%	8	4.5%	5	2.7%
	Anxiety	2	0.6%	.	.	.	.

Source: Studies TAF112582, part 1 and 2, ADAE and ADSL datasets, JUMP Clinical v. 12.2.0

Clinical Reviewer's Comment: The clinical data from TAF112582 part 1 &2 support the inclusion of dizziness and insomnia in the TQ USPI.

Neurologic adverse events occurring in the integrated summary of safety database (ISS)

In the ISS database, 22 studies (TQ single- and multiple-dose studies) of TQ regardless of duration of treatment reported neurological adverse events. Headache and dizziness were common adverse events across all doses of TQ. Headache (13%), dizziness (3%), and lethargy (2%) were the most common adverse events at doses of TQ > 300mg.

Dizziness was more common in subjects treated with TQ 300mg as compared to placebo/ CQ groups, 62(8%) vs. 24(3%), respectively, (Table 78). The incidence of headache in the TQ 300mg (98, 12%) groups was lower than in the CQ/placebo (149, 19%) groups. Other neurological adverse events occurring at < 1.0% in the TQ 300mg group included migraine, dysgeusia, somnolence, syncope, tremor, balance disorder, and depressed level of consciousness.

Table 78. ISS: Neurological Adverse Events by Treatment Arms

	>300mg Total TQ	Placebo or CQ	300mg Total TQ	<300mg Total TQ
	N=2897	N=794	N=810	N=392

System Organ Class	Preferred Term	Count	%	Count	%	Count	%	Count	%
Nervous system disorders	Headache	375	12.9%	149	18.8%	98	12.1%	71	18.1%
	Dizziness	92	3.2%	24	3.0%	62	7.7%	17	4.3%
	Lethargy	56	1.9%	.	.	.	.	.	.
	Somnolence	22	0.8%	1	0.1%	3	0.4%	.	.
	Dysgeusia	18	0.6%	1	0.1%	.	.	.	.
	Migraine	3	0.1%	4	0.5%	3	0.4%	2	0.5%
	Paresthesia	7	0.2%	.	.	.	.	1	0.3%
	Syncope	3	0.1%	.	.	2	0.2%	.	.
	Hypoesthesia	4	0.1%	1	0.1%	.	.	.	.
	Sinus headache	4	0.1%	1	0.1%	.	.	.	.
	Tremor	3	0.1%	.	.	1	0.1%	.	.
	Sciatica	2	0.1%	.	.	.	.	1	0.3%
	Coordination abnormal	2	0.1%	.	.	.	.	.	.
	Hyperesthesia	1	0.0%	.	.	.	.	1	0.3%
	Post herpetic neuralgia	2	0.1%	.	.	.	.	.	.
	Tension headache	2	0.1%	.	.	.	.	.	.
	Amnesia	1	0.0%	.	.	.	.	.	.
	Balance disorder	.	.	.	.	1	0.1%	.	.
	Burning sensation	.	.	.	.	.	.	1	0.3%
	Depressed level of consciousness	.	.	.	.	1	0.1%	.	.
	Disturbance in attention	1	0.0%	.	.	.	.	.	.
	Dizziness postural	.	.	1	0.1%	.	.	.	.
	Dysesthesia	.	.	.	.	.	.	.	.
	Head discomfort	1	0.0%	.	.	.	.	.	.
	Loss of consciousness	.	.	1	0.1%	.	.	.	.
	Muscle contractions involuntary	1	0.0%	.	.	.	.	.	.
	Presyncope	1	0.0%	.	.	.	.	.	.
	Trigeminal neuralgia	1	0.0%	.	.	.	.	.	.
	Visual field defect	1	0.0%	.	.	.	.	.	.

This analysis includes data from 22 studies, TAF033, TAF112582, TAF030, TAF049, TAF043, TAF057, TAF006, TAF116564, TAF058, TAF114582, TAF047, TAF040, TAF106491, TAF003, 201807, 200951, TAF001, TAF015, TAF014, TAF044, TAF022, TAF110027.

*The placebo group includes healthy volunteers treated with placebo and *P. vivax* subjects treated with CQ alone in studies TAF112582 and TAF047.

Source: ISS, ADAE and ADSL datasets, JUMP Clinical v. 12.2.0

Clinical reviewer's comment: Headache and dizziness were common neurological events across studies of TQ single dose and multiple dose studies and are probably associated with TQ. A variety of other neurological adverse events occurred relatively infrequently at < 1% in the single and multiple dose studies and are more difficult to attribute any causality. Neurobehavioral studies in rats have not demonstrated neurological adverse effects in TQ - treated animals (TQ 125 to 500mg/kg) versus controls and no significant lesions were noted on histopathology of the brains of these animals. See section 5.

Psychiatric Adverse Events occurring in the ISS database

In the ISS database, among 16 studies (TQ single- and multiple-dose studies) insomnia was the most common adverse event across all doses of TQ. Insomnia (15, 1.9%), abnormal dreams (1,

0.1%), and anxiety/anxiety disorder (2, 0.2%) were reported in 810 subjects who received TQ 300mg, Table 79. A variety of psychiatric adverse events with incidences < 1.0% were reported in of patients in the multiple dose studies (TQ > 300mg); among these studies was Study 033 which was a trial in deployed military personnel who received weekly doses of TQ versus MQ for up to six months for malaria prophylaxis.

Table 79. ISS: Psychiatric Disorders by Treatment Arms

		>300mg Total TQ		300mg Total TQ		Placebo or CQ		<300mg Total TQ	
		N=2897		N=810		N=794		N=392	
System Organ Class	Preferred Term	Count	%	Count	%	Count	%	Count	%
Psychiatric disorders	Insomnia	27	0.9	15	1.9	8	1.0	6	1.5
	Abnormal dreams	6	0.2	1	0.1	.	.	.	.
	Euphoric mood	3	0.1	.	.	.	.	.	.
	Sleep disorder	3	0.1	.	.	.	.	.	.
	Agitation	2	0.1	.	.	.	.	.	.
	Anxiety	.	.	2	0.2	.	.	.	.
	Anxiety disorder	2	0.1	.	.	.	.	.	.
	Depressed mood	2	0.1	.	.	.	.	.	.
	Depression	2	0.1	.	.	.	.	.	.
	Irritability	1	0.0	.	.	.	.	1	0.3
	Nightmare	2	0.1	.	.	.	.	.	.
	Alcoholic hangover	1	0.0	.	.	.	.	.	.
	Bipolar disorder	1	0.0	.	.	.	.	.	.
	Disinhibition	1	0.0	.	.	.	.	.	.
	Mood altered	1	0.0	.	.	.	.	.	.
	Neurosis	1	0.0	.	.	.	.	.	.
	Panic attack	1	0.0	.	.	.	.	.	.
	Psychotic disorder	1	0.0	.	.	.	.	.	.
	Stress	1	0.0	.	.	.	.	.	.
	Tic	1	0.0	.	.	.	.	.	.
	Suicide attempt	1	0.0						

This analysis includes data from 16 studies, TAF033, TAF112582, TAF030, TAF049, TAF043, TAF057, TAF006, TAF116564, TAF058, TAF114582, TAF047, TAF040, TAF106491, 200951, TAF001, TAF014.
*The placebo group includes healthy volunteers treated with placebo and *P. vivax* subjects treated with CQ alone (placebo-equivalent) in studies TAF112582 and TAF047.
Source: NDA 210795, ISS, ADAE and ADSL datasets, JUMP Clinical v. 12.2.0

Clinical reviewer's comment: Insomnia is a known adverse reaction associated with MQ but not with PQ. The suicide attempt case was confounded because the patient was depressed about martial problems, had suicidal ideation prior to taking TQ, and the suicide attempt occurred when he was intoxicated with alcohol.

Ophthalmologic Adverse Events

Adverse Events occurred in ≤ 1.0% of patients in the pooled analysis of the TQ 300mg in the three efficacy and safety trials, Table 80. Five (1%) patients reported blurred vision: three in TAF112582 part 2 and two in TAF116564 within the first 29 days of the trial and all resolved. Blurred vision was more common in the CQ arm than the TQ+CQ arm. In study TAF112582, part

2, there was one case of unilateral Grade 1 vortex keratopathy in the TQ+CQ group, which was not associated with vision changes. One male patient with a history of untreated hypertension in the TQ+CQ group presented with anterior ischemic optic neuropathy which resolved in 2 days and was considered as unrelated to TQ + CQ. No retinal abnormalities were reported in the TQ 300mg + CQ group.

Table 80.TAF112582 & TAF116564: Ophthalmologic Treatment Emergent Adverse Events

	Placebo(CQ) - controlled Trials: TAF112582, Part 1 & 2. N=683			Primary Efficacy and Safety Trials: TAF112582 part 1& 2 and TAF116564. N=747	
Preferred Term	TQ 300mg +CQ N=317	CQ only N= 187	PQ+CQ N= 179	TQ 300mg + CQ N = 483	PQ +CQ N = 264
Chorioretinal disorder	-	-	-	0 (0.0%)	1 (0.3%)
Conjunctivitis viral	-	-	-	1 (0.2%)	0
Optic ischemic neuropathy (anterior)	1(0.3%)	0	0	1 (0.2%)	0
Photophobia	-	-	-	1 (0.2%)	0
Vision blurred	3 (0.9%)	4(2.1%)	3 (1.6%)	5 (1.0%)	3 (0.9%)
Visual field tests abnormal	-	-	-	1 (0.2%)	1 (0.3%)

Source: StudiesTAF112582 and TAF116564, ADSL and ADAE datasets, JReview 11.0

Clinical Reviewer's Comment: *A review of ophthalmologic safety of TQ single-dose was performed by the Division of Transplant and Ophthalmologic Products (DTOP). The ophthalmology reviewer, William Boyd, M.D. notes that "Ophthalmic Events and Assessments" in the ISS were not particularly useful for drawing conclusions regarding single-dose TQ use because it contained combined data from single-dose and multi-dose trials with TQ and contains only a minimal discussion of the interim data for Study 201807. 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 pharmacodynamics 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). The primary endpoint was the proportion of subjects treated with TQ who developed significant protocol-defined retinal changes from Baseline to Day 90.*
The ophthalmology team's completed review of Study 201807 concluded that the results do not indicate any clinically significant ocular risk from the use of TQ 300 mg single-dose treatment and there are no recommended labeling revisions. See ophthalmologic consult review (5/11/2018) by William Boyd, M.D. in DARRTS.

Renal and Urinary Adverse Events

The incidence of renal and urinary adverse events in the three key trials TAF112582 part 1& 2 and TAF116564 was < 2.0%, Table 81. There were no serious adverse events or adverse events that led to discontinuation from study drugs or withdrawal from the trials. The most frequently

reported AEs in the TQ+CQ group were dysuria and proteinuria which had similar incidences across the three treatment groups.
The proposed TQ 300 mg single-dose was associated with small reversible increases in serum creatinine. For example, in TAF112582, part 2, serum creatinine was mildly increased in 2(0.6%) subjects in the TQ+CQ group but not in the PQ+CQ or CQ treatment groups. Mild reversible elevations in mean creatinine concentrations (±SD) compared with baseline were noted in the TQ+CQ group at Day 5 (3.61±18.04 µmol/L) and Day 8 (2.95±19.73 µmol/L). Elevations in creatinine were not considered clinically significant. There were no clinically significant changes from baseline in eGFR in any treatment group.

Table 81. TAF112582 & TAF116564: Renal and Urinary Treatment Emergent Adverse Events

	Placebo (CQ) - controlled Trials: TAF112582, Part 1 & 2. N=683			Primary Efficacy and Safety Trials: TAF112582 part 1& 2 and TAF116564. N=747	
Preferred Term	**TQ 300mg +CQ N=317**	**CQ N=187**	**PQ +CQ N=179**	**TQ 300mg +CQ N=483**	**PQ +CQ N=264**
Dysuria	2 (0.6%)	3(1.6%)	1(0.6%)	6 (1.2%)	3 (1.1%)
Glycosuria	0	0	0	0	1 (0.4%)
Nephrolithiasis	0	0	0	1 (0.2%)	0
Proteinuria	2(0.6%)	1(0.5%)	1(0.6%)	2 (0.4%)	1 (0.4%)
Glycosuria	0	0	1(0.6%)	0	0
Urine flow decreased	0	0	1(0.6%)	0	1 (0.4%)

Source: StudiesTAF112582 and TAF116564, ADSL and ADAE datasets, JReview 11.0

Clinical reviewer's Comment: No safety signal for renal adverse effects was found in the three clinical trials.

Creatinine Phosphokinase (CPK) Elevations

Subjects in each of the three treatment groups had CPK elevations > 5x ULN (grade 3 severity) during the study. CPK elevations were more common in the CQ treatment group, Table 82.
In TAF112582, part 1, isolated cases of clinically significant elevations in serum CPK (> 5x ULN) were noted in several subjects. Overall, there was no treatment-emergent trend for increases in serum CPK in any treatment group. The CPK elevations occurred on or after Day 29, except for one subject in the TQ 300mg + CQ group whose CPK levels were elevated at Day 3 and returned to baseline by Day 8.
In TAF112582, part 2, increases in CPK levels were associated with strenuous exercise or other muscle injury. Three subjects had possible drug-related events of CPK increased: 1 subject (<1%) in the CQ alone group and 2 subjects (<1%) in the TQ+CQ group. All CPK elevations resolved without specific medical intervention.

Table 82. TAF112582, part 1 & 2: CPK Elevations by Treatment Group

Creatine phosphokinase	**TQ 300mg + CQ N=317**	**CQ N=187**	**PQ+CQ N=179**
CPK Increase	11(3.5%)	10 (5.3%)	7(3.9%)
CPK increase, Day 1 to 29	5 (1.6%)	5 (2.7%)	1(0.6%)

Source: TAF112582 part 1&2 ADLAB datasets, JReview 12.0

Clinical Reviewer's Comment: CPK elevation is not a labeled adverse event for CQ, PQ, or MQ. Myopathy is associated with chronic use of CQ. In the TQ trials, elevations in CPK were observed in all treatment groups and were related to strenuous exercise and other muscle injury in the majority of patients but remained unexplained in some patients. Elevations in CPK were not associated with renal injury or rhabdomyolysis. CPK elevation is not considered a significant safety signal associated with TQ but should be listed in the Adverse reactions section of the label.

9.1.6.Safety Analyses by Demographic Subgroups

Safety analyses by gender, age, and race, country and study site were performed focusing on AEs by body system organ class and TEAEs using dictionary derived terms. No specific pattern of concern was identified in the safety analyses by race, gender, and age.

Pruritus which was probably associated with CQ, although similar in incidence across treatment arms, was more commonly reported in American Indian subjects than in other races; however, American Indian was also the most common race in the clinical trials.

Clinical Reviewer's Comment: CQ-induced pruritus appears to be more common in patients with dark skin.[25] Host-parasite interaction may play a role in the development of pruritus and an association of pruritus with high parasitemia and allergy history has been reported and patients with previous CQ-induced pruritus may have a high risk for developing pruritus.[26]

Study Sites/Country: In study TAF112582 part 2, Hgb decreases reported as SAEs (pre-defined in the study protocol) were not reported at the second highest enrolling site, # (b) (6), in Peru as compared to the 14 cases at the highest enrolling site # (b) (6) in Brazil.

Clinical Reviewer's Comment: Serious adverse events (as pre-defined in the study protocol for TAF112582 part 2) were not reported at the second highest enrolling site, # (b) (6), in Peru as compared to the 14 SAEs (decreases in Hgb) at the highest enrolling site # (b) (6) in Brazil. This reviewer did not find additional information in the NDA that would explain the imbalance in reporting of SAEs between the two sites and an IR was sent to GSK for their perspective. The Applicant noted in their response dated 6/15/2018, that they did not believe the difference in SAE reports was related to any issue with the conduct of the study or reporting methods in

[25] Aghahowa, S.E., Obianwu, H.O., Isah, A.O., *et al*. Chloroquine-induced pruritus. Indian Journal of Pharmaceutical Sciences 2010;72: 283–289.

[26] Ballut PC, Siqueira AM, Orlando Aline CB, *et al*. Prevalence and risk factors associated to pruritus in *Plasmodium vivax* patients using chloroquine in the Brazilian Amazon. Acta Tropica 2013;128: 504–508.

either the Iquitos, Peru (# (b) (6)) or Manaus, Brazil (# (b) (6)) sites. They believe that the observed Hgb declines were likely related to "an imbalance in baseline Hgb and other baseline laboratory values between the two sites. This resulted in an increased frequency of Hgb declines ≥3g/dL in subjects at the Manaus, Brazil (# (b) (6)) site during the first 15 days of treatment." Planned routine clinical inspections by OSI is underway at sites in Brazil (# (b) (6)) and Thailand (# (b) (6)); however, the planned clinical inspection at the site in Peru (# (b) (6)) was canceled due problems with travel logistics.

Overall, no specific pattern of adverse events was identified in the safety analyses by gender, age, race, country/ study site.

9.1.7.Specific Safety Studies/Clinical Trials

TAF 116564 was conducted to evaluate hematological safety parameters in patients with *P. vivax* malaria who received a single dose, TQ 300mg + CQ. TAF 116564 is a randomized (2:1), double-blind, double-dummy, comparative multicenter study to assess incidence of hemolysis, safety, and efficacy of TQ+CQ versus PQ+CQ in the treatment of subjects with *P. vivax* malaria. The study design and demographics are discussed in section 7.2.3. The design of TAF116564 is similar to the design of the phase 3 trial, TAF112582, part 2 except that there is no CO only arm. The dosing regimens for study drugs are summarized in Table 83.

Table 83. TAF 116564: Dosing Regimens for TQ, PQ, and CQ

Treatment Arm	Day 1	Day 2	Day 3	Days 4 – 15
tafenoquine	2×CQ 300mg	2×CQ 300mg + 2×TQ 150mg + 1×PQ placebo	1×CQ 300mg + 1×PQ placebo	1×PQ placebo
primaquine	2×CQ 300mg	2×CQ 300mg + 2×TQ placebo + 1×PQ 15mg	1×CQ 300mg + 1×PQ 15mg	1×PQ 15mg
Total number of capsules/tablets per treatment arm	**2 tablets**	**4 tablets + 1 capsule**	**1 tablet + 1 capsule**	**1 capsule × 12 days**

NOTE: subjects may begin blinded study medication (TQ or PQ and corresponding placebo) on Day 1 or Day 2 of the study.

Source: TAF 116564 clinical study protocol, section 5.18

Study Endpoints

The primary safety endpoints were:

- occurrence of clinically relevant hemolysis in all subjects, defined as a decrease in hemoglobin of ≥30% or > 3 g from baseline, or a drop in hemoglobin to below 6.0 g/dL.
- occurrence at clinically relevant hemolysis, as defined above, in a subgroup of Thai female subjects with diagnosed with moderate G6PD deficiency (40 to 70% enzyme

activity).

Male and female patients with smear positive *P. vivax* malaria were included in the trial. Patients with G6PD deficiency with less than 40% enzyme activity were excluded from the trial for safety reasons related to potential for aminoquinoline drugs to cause hemolytic anemia.

RESULTS

Study Visits

Compliance with attendance at study visits was > 95% over the 180-day study period, Table 84. Three patients were withdrawn from the trial.

Table 84. TAF116564: Study Visits

Visit Number	Visit Name	Total N	PQ+CQ	TQ+CQ
		N=251(100%)	N=85(100%)	N=166(100%)
10	DAY 1	251	85	166
20	DAY 2	251	85	166
30	DAY 3	251	85	166
50	DAY 5	251	85	166
60	DAY 8	248	84	164
70	DAY 11	248	84	164
80	DAY 15	249	84	165
90	DAY 22	248	84	164
100	DAY 29	247	84	163
110	DAY 60	244	83	161
120	DAY 90	243	82	161
130	DAY 120	241	81	160
135	DAY 150	243	82	161
140	DAY 180	243	83	160
150	WITHDRAWAL	3	1	2
160	EOS	251	85	166
200	CLIN STOP	5	1	4

Visits #: Day of study. Visit 10: Day 1; Visit 30: Day 3; Visit 50: Day 5; Visit 60: Day 8; Visit 70: Day 11; Visit 80: Day 15; Visit 90: Day 22; Visit 100: Day 29; Visit 110: Day 60; Visit 120: day 90; Visit 130: Day 120; Visit 135: day 150; Visit 140: Day 180; Visit 150 Withdrawal; Visit 160: EOS
Source: TAF116564, Demographic datasets, JUMP Clinical 12.2.0

Patient Disposition

Reasons for withdrawal from the trial or for discontinuation of study medications are outlined in

Table 85. No subjects withdrew from the study due to AEs. The most common reason for withdrawal in both treatment groups was lost to follow-up. Discontinuation from study medications due to an adverse event occurred in 1(0.6%) patient in the TQ 300mg+CQ and 1(1.2%) patient in the PQ+CQ group. Four subjects fulfilled protocol-defined stopping criteria. Three subjects (2%) in the TQ+CQ group discontinued study medication because they fulfilled Hgb stopping criteria.

Table 85. TAF116564: Patient Disposition

Standardized Disposition Term	TQ 300mg +CQ N=166 (%)	PQ +CQ N= 85 (%)
Lost to Follow-Up	4 (2.4%)	2 (2.4%)
Subject Reached Protocol-Defined Stopping Criteria	3 (1.8%)	1 (1.2%)
Withdrawal by Subject	2 (1.2%)	0
Adverse Event	1 (0.6%)	1 (1.2%)
Physician Decision	1 (0.6%)	0
Other	1 (0.6%)	0

Source: TAF116564, ADSL and ADAE datasets, JReview 11.0

Analysis of Safety Results

The safety population (N= 251) included all patients treated with TQ+CQ (n=166) or PQ+CQ (n=85).

Coding of Adverse Events

All adverse events in the ADAE datasets are listed as treatment emergent adverse events. The coding of AEs was analyzed and all reported adverse events (AETERM) appear to be appropriately matched to preferred terms (AEDECOD) in the reviewer's opinion. The reported term "*acarodermatitis*" was appropriately translated and coded to the preferred term, scabies.

Treatment Emergent Adverse Events

Adverse events occurred in approximately 70% of patients, Table 86. Serious adverse events occurred < 5% of patients but were more common in the TQ+CQ treatment group than in the PQ+CQ group, (4% vs. 1%). The safety review will focus on treatment emergent adverse events related to the primary and secondary safety endpoints for hematologic adverse events.

Table 86. TAF116564: Treatment Emergent Adverse Events - Safety population

	TQ 300mg + CQ N=166 (100%)	PQ + CQ N=85 (100%)
Any adverse event	119 (72 %)	64 (75%)
Any serious adverse	6 (4%)	1 (1%)
Any fatal and serious adverse event	0	0
Any adverse events leading to study withdrawal	0	0
Any adverse events leading to discontinuation of study drug	1(<1%)	1(1%)
Any drug-related adverse event	14 (8%)	11 (13%)
Source: TAF116564, ADSL and ADAE datasets, JReview 11.0		

Common Adverse Events

The most common adverse events occurring in > 5% of patients in the TQ+CQ group during the first 29 days of the trial were pruritus, dizziness, headache, nausea, and vomiting, Table 87. Pruritus was more common in the PQ+CQ (19 patients, 22%) than TQ+CQ. Pruritus is known to be associated with CQ but has also been reported with PQ. Pruritus was not associated with

other allergic symptoms. The incidence of the other four adverse reactions dizziness, headache, nausea, and vomiting were similar between the two treatment groups. Decreases in Hgb levels occurred in 2% of patients in the TQ+CQ arm and are discussed under serious adverse events.

Table 87. Study TAF116564: Common Adverse Events Day 1 to Day 29

	TQ+CQ		PQ+CQ	
	N=166		N=85	
Preferred Term	**Count**	**%**	**Count**	**%**
Pruritus	20	12.0%	19	22.4%
Dizziness	25	15.1%	12	14.1%
Headache	19	11.4%	9	10.6%
Nausea	16	9.6%	6	7.1%
Vomiting	11	6.6%	5	5.9%
Abdominal pain upper	8	4.8%	1	1.2%
Diarrhea	6	3.6%	3	3.5%
Asthenia	4	2.4%	4	4.7%
Nasopharyngitis	6	3.6%	1	1.2%
Urinary tract infection	5	3.0%	2	2.4%
Hemoglobin decreased	4	2.4%	1	1.2%
Pharyngitis	2	1.2%	2	2.4%
Back pain	1	0.6%	2	2.4%
Pyrexia	2	1.2%	1	1.2%
Cellulitis	2	1.2%	.	.
Cough	1	0.6%	1	1.2%
Dysuria	2	1.2%	.	.
Skin infection	1	0.6%	1	1.2%
Abdominal pain	.	.	1	1.2%
Anxiety	.	.	1	1.2%
Arthralgia	1	0.6%	.	.
Blood creatine phosphokinase increased	1	0.6%	.	.
Hypertension	1	0.6%	.	.
Myalgia	1	0.6%	.	.

Source: TAF116564, ADAE dataset, JUMP v. 12.2.0

Serious Adverse Events

There were no deaths in the trial. Six (3.6%) patients in the TQ+CQ group experienced serious adverse events. Four patients experienced a decrease in Hgb levels and one patient each experienced pyrexia and pneumonia, Table 88.

Table 88. TAF116564: Serious Adverse Events by Treatment Arm - Safety Population

Serious Adverse Events		**Treatment Arm**			
		TQ+CQ		**PQ+CQ**	
		N= 166		**N=85**	
System Organ Class	**Preferred Term**	**Count**	**%**	**Count**	**%**
Investigations	Hemoglobin decreased	4	2.4%	1	1.2%
General disorders and administration site conditions	Pyrexia	1	0.6%	.	.
Infections and infestations	Pneumonia	1	0.6%	.	.

Source: TAF116564, ADAE dataset, JUMP Clinical v.12.2

Case narratives for patients who experienced SAEs are discussed below:

Pyrexia

A 46-year-old Hispanic female was hospitalized on study Day 9 (7 days posttreatment with TQ+CQ) with pyrexia, chills, and headache which remained undiagnosed. Results of repeat malaria smear was not reported. Patient recovered study on Day 11 without additional antimalarial treatment. This adverse event does not appear to be associated with study drugs.

Pneumonia

A 58-year-old Hispanic male presented on study Day 39 with community acquired bacterial pneumonia which responded to ceftriaxone IV x 4 days followed by amoxicillin-clavulanate x 3 days. This adverse event does not appear to be associated with study drugs.

Pregnancy

There was one pregnancy case report (prospective): Subject # (b) (6) was a 35-year-old Hispanic/Latino female who started blinded investigational product on Study Day 2 for *P. vivax* malaria. Concomitant medication included CQ and medroxyprogesterone acetate (Depo Provera). The subject's last menstrual period was on study Day 24 and estimated date of delivery was study Day 304. On Study Day 291, after 39 weeks gestation, the subject gave birth to a live male infant by normal vaginal delivery and weight 3440 g, height 50.0 cm. Apgar score 9,10.

Decreases in Hgb

Hemolysis was pre-defined in the protocol as a decrease in Hgb >3.0 g/dL or ≥ 30% from baseline or an overall drop in Hgb to below 6.0 g/dL (same as TAF112582 part 2). Laboratory results for the 5(3%) male patients who experienced drops in hemoglobin > 3.0 g /dL from baseline are summarized in Table 89. All five patients had normal G6PD enzyme activity (site cut-off = 5.54 units/g Hgb). The maximum drop was 5.3g/dL in a patient who dropped Hgb from 19.2 to 13.9 g/dL. No symptoms of anemia were reported. No oral iron supplementation, intravenous fluids or blood transfusions were administered. Small increases in reticulocyte counts were observed in both treatment groups from Day 8 to Day 29, in a pattern consistent with recovery from *P. vivax* malaria. One patient (# (b) (6)) had increased reticulocytes outside the normal range. All patients recovered.

Table 89. TAF 116564: Serious adverse events, decreases in hemoglobin > 3 g /dL from baseline

Site / Subject no.	Sex/ Age	Rx	Hgb g/dL Baseline	Hgb g/dL nadir/ Day #	Hgb g/ dL at end of SAE	Reticulocyte % Min / Max	Total bilirubin, mg/dL Min /Max	Urine Bili	Urea mg /dL min/max	Creat. mg /dL	Action taken with study drugs
(b) (6)	M / 21y	TQ + CQ	15.1	12.1 (Day 5)	13.3 (Day 10)	0.5 /3.18	0.7 / 2.45	Neg	26 /42	0.8 /1.2	D/C
	M / 72y	TQ +	15.8	12.6 (Days	13.5 (Day	0.2 / 2.08	0.25 / 0.52	Neg	7 /41	1.4 /1.1	D/C

Site / Subject no.	Sex/ Age	Rx	Hgb g/dL Baseline	Hgb g/dL nadir/ Day #	Hgb g/ dL at end of SAE	Reticulocyte % Min / Max	Total bilirubin, mg/dL Min /Max	Urine Bili	Urea mg /dL min/max	Creat. mg /dL	Action taken with study drugs
		CQ		8 & 11)	15						
(b) (6)	M / 34y	TQ + CQ	15.4	12.4	13.6 (Day 15)	1.07 / 2.39	0.43 / 2.78	Neg	21 /34	0.9 /1.2	D/C
	M / 58y	TQ + CQ	19.2	13.9 (Day 8)	14.1 (Day 15	0.44 / 1.66	0.34 / 1.45	Neg	16 /43	0.8 /1.3	D/C
	M / 64y	PQ + CQ	12.6	9.5 (Day 11)	10.2 (Day 22)	1.0 / 2.02	0.45 / 1.56	Neg	25 /75	0.9 /1.7	D/C
Normal ranges approx.	-		*12.5-15.5 g/dL*	*12.5-15.5 g/dL*	*12.5-15.5 g/dL*	*0.56-2.72 %*	*0.01-1.3 mg/dL*	*Neg*	*10 -45*	*0.5 /1.2*	

Hgb: Hemoglobin; M: male; y: years of age; D/C: discontinued; Rx: Treatment arm; Creat: creatinine.
*Patient #(b) (6): Total Bilirubin declined from 2.45mg/dL on Day 1 to 0.75mg/dL on Day 10.
†Patient #(b) (6): Total Bilirubin declined from 2.78mg/dL on Day 1 to 0.43mg/dL on Day 15.
§ Patient #(b) (6): Total Bilirubin declined from 1.56 mg/dL on Day 1 to 0.56mg/dL on Day 15; Urea trended down from 70mg/dL on Day 1 to 25mg/dL on Day 15.
Source: NDA 210795, TAF116564, ADAE and ADLAB dataset, JReview 12.0

Decreases in Hgb of > 2.0g/dL occurred in approximately 20% of patients in both treatment arms, Table 90. Decreases in Hgb of > 3.0g/dL occurred in approximately 2% of patients. There was no significant difference in the mean change in Hgb g/dL from baseline between study arms and across study visits.
There were no clinically significant changes in other markers of hemolysis such as reticulocytosis or bilirubinemia (incr. indirect bilirubin) observed posttreatment or throughout the trial.

Table 90. TAF116564: Hemoglobin (g/dL) decrease from baseline in subjects with *P. vivax* malaria – Safety population

Hemoglobin (Hgb) - decrease from baseline	TQ 300mg +CQ N=166, n(%)	PQ 15 mg x 14d + CQ N=85, n(%)
> 2g/dL to ≤ 3	32 (19)	14 (16)
> 3g/dL or ≥ 30%	4 (2)	1 (1)

Source: TAF116564, ADAE dataset, JReview v. 11.0;

A greater proportion of patients experienced a decline in Hgb in the TQ 300mg + CQ arm than in the PQ+CQ, (Table 91). Hemolysis due to study drugs, PQ or TQ, could not be assessed in G6PD deficient patients due to low recruitment (one G6PD deficient patient was enrolled). Other hematological adverse events, included elevated bilirubin levels > 2 mg/dL in 2 patients on Day 1 which improved on TQ+CQ treatment and were associated with *P. vivax* malaria.

Table 91. TAF116564: Hematological Adverse Events

Adverse Event Preferred Term	TQ300mg + CQ N=166	PQ + CQ N=85
Hemoglobin decreased	4 (2.4%)	1 (1.2%)
Bilirubin increased	1 (0.6%)	0
Hyperbilirubinemia	1(0.6%)	1(0.6%)
Anemia	0	1(0.6%)
Fatigue	1(0.6%)	1(0.6%)
Tachypnea	1(0.6%)	0

Source: TAF116564, ADAE dataset, JReview v. 11.0

Clinical Reviewer's Comment: The 8-aminoquinolines, of which PQ and TQ are members, are associated with hemolysis/hemolytic anemia in patients with G6PD deficiency. Reversible declines in Hgb were observed in G6PD normal patients in this safety trial as was seen in the placebo(CQ)- controlled trials.
Declines in hemoglobin is associated with malaria which confounds an attribution of causality to TQ +CQ in the trials. The study drugs PQ and TQ could have exacerbated hemolysis, however the pattern of improvement seen clinically and in the hematologic parameters (Hgb, bilirubin, and reticulocytes) on treatment is consistent with recovery from P. vivax malaria. In this G6PD normal study population, the declines in Hgb were likely due to lysis of red blood cells due primarily to P. vivax infection. Rehydration causing increased intravascular volume may have contributed to the observed decrease in Hgb.

Two subjects, one in each arm, had Hgb decreases ≤ 2.0g/dL but experienced nadirs Hgb < 8.0g/dL and were not reported as adverse events.

Case narrative – Decreases in Hgb, TQ+CQ arm
Subject # (b) (6) (randomized to TQ+CQ) was a 45-year-old Native American male from Colombia with a Hgb of 9.3 g/dL at screening, which fell to 7.3 g/dL on Day 3. No concomitant intravenous fluids were administered. His G6PD activity at screening was 10.1 IU/g Hgb (normal). No blood transfusion was required. The Hgb normalized without specific medical intervention and study treatment was completed without interruption.

Clinical Reviewer's Comment: G6PD testing prior to TQ administration is essential so that hemolytic anemia is avoided. Monitoring of hematologic parameters (e.g., Hgb, reticulocytes) is advised, especially in patients with P. vivax malaria who are anemic at baseline.

Other Hematology Laboratory Tests
There were no clinically significant differences between the treatment groups in the proportions of subjects with abnormal values in hematology parameters other than Hgb during the study, (Table 92). Eosinophils counts were elevated at a similar frequency (18 to 19%) across both arms. Elevated eosinophil counts may be related to the history of helminthic infections reported in 20 to 22% of patients in both study arms. Hookworm infection is

associated with eosinophilia (usually mild), and it was the only helminth infections reported post baseline in 7(4%) and 1(1%) TQ+CQ and PQ+CQ patients, respectively.

Table 92. TAF116564: Subjects with abnormal hematology laboratory evaluations

Blood Laboratory Test, n (%)	TQ+CQ (N=166)	PQ+CQ (N=85)
Eosinophils >1.5 x10^9/L	32 (19)	15 (18)
Leukocytes <2 x10^9/L	0	0
Lymphocytes <0.5 x10^9/L	8 (5)	1 (1)
Lymphocytes >4 x10^9/L	11 (7)	4 (5)
Neutrophils, segmented <1 x10^9/L	5 (3)	3 (4)
Platelets <50 x10^9/L	13 (8)	8 (9)
Reticulocytes >1xULN	80 (48)	39 (46)
Methemoglobin >10%	2 (1)	3 (4)

Source: Table 3.27

Source: NDA 210795, TAF116564, Applicant's Table 26 and Table 3.27.

Clinical reviewer's comment: Pseudo-eosinophilia secondary to malaria could be another possible cause of elevation eosinophil counts. Elevated eosinophil counts were not significant in the healthy volunteer studies of single-dose TQ administered without CQ.

Reticulocyte Counts

Small increases in reticulocyte counts were observed in both treatment groups from Day 8 to Day 29, which are consistent with recovery from *P. vivax* malaria.

Methemoglobinemia

Methemoglobinemia was more common in the PQ+CQ group than the TQ+CQ. Sixteen (9.6%) patients in the TQ 300mg +CQ and 31(36.5%) in the PQ+CQ group experienced MetHb ≥ 5% (normal < 3%). A larger proportion of patients in the PQ+CQ experienced increases in MetHb > 5% from baseline levels than in the TQ+CQ group, i.e., 28 (33%) versus 11 (7%), respectively, (Table 93). Five patients, 2(1.2%) in the TQ+CQ and 3(3.5%) in the PQ+CQ, experienced MetHb ≥ 10%, however, all patients were asymptomatic.

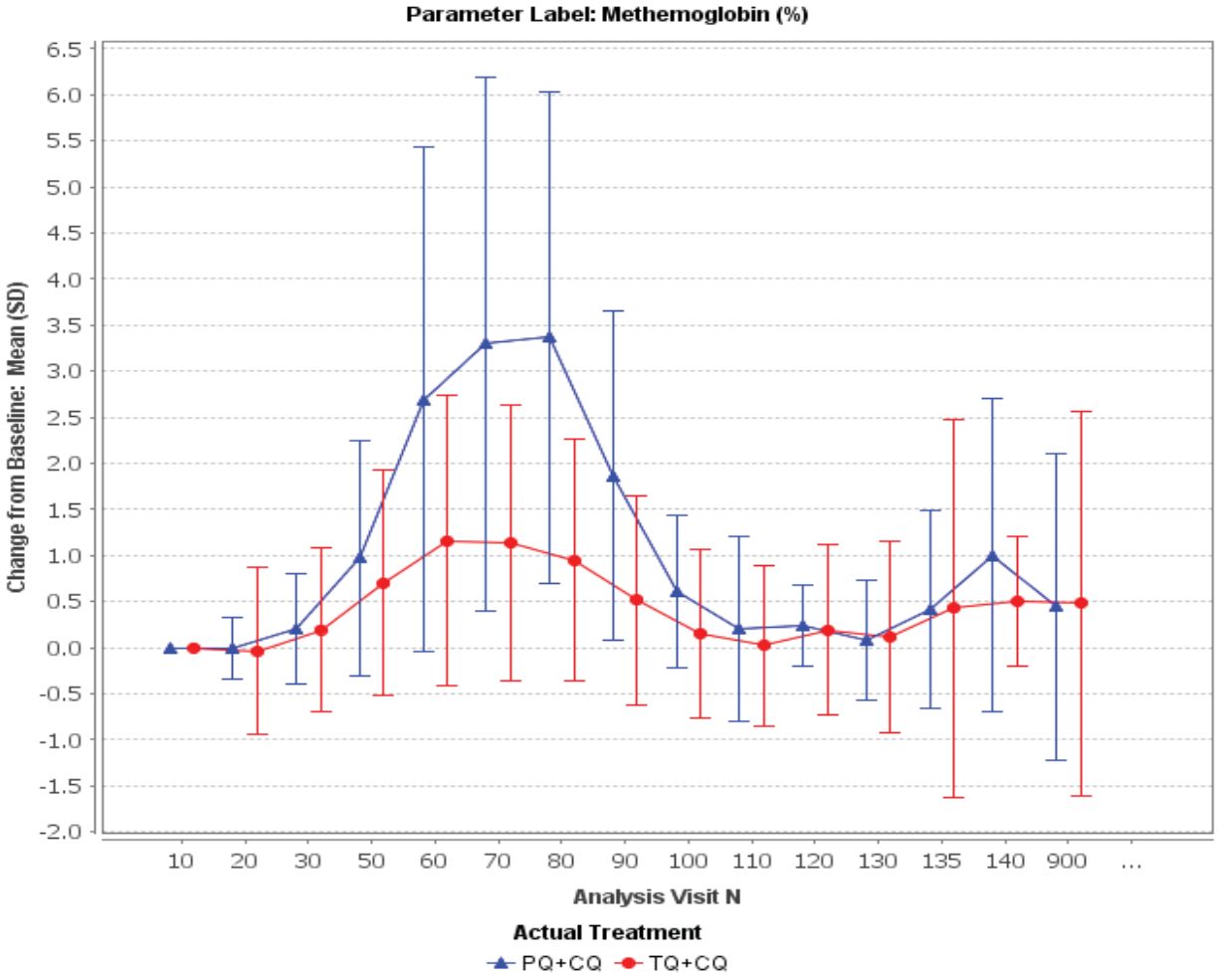
Table 93. TAF116564: Methemoglobin % changes from baseline – Safety population

PARAMETER	Parameter Result	TQ 300mg +CQ N=166	PQ+CQ N=85
Methemoglobin (%) Max. actual value	Methemoglobin >= 1% [n (%)]	146 (88.0%)	83 (97.6%)
	Methemoglobin >= 2% [n (%)]	89 (53.6%)	69 (81.2%)
	Methemoglobin >= 3% [n (%)]	54 (32.5%)	54 (63.5%)
	Methemoglobin >= 5% [n (%)]	16 (9.6%)	31 (36.5%)
	Methemoglobin >=10% [n (%)]	2 (1.2%)	3 (3.5%)
Methemoglobin (%) Max change from baseline	increase Methemoglobin >= 1% [n (%)]	105 (63.3%)	77 (90.6%)
	increase Methemoglobin >= 2% [n (%)]	61 (36.7%)	60 (70.6%)
	increase Methemoglobin >= 3% [n (%)]	30 (18.1%)	48 56.5%)
	increase Methemoglobin >= 5% [n (%)]	11 (6.6%)	28 (32.9%)

PARAMETER	Parameter Result	TQ 300mg +CQ N=166	PQ+CQ N=85
	increase Methemoglobin >=10% [n (%)]	2 (1.2%)	1 (1.2%)

The maximum change in mean MetHb% from baseline by study visit are shown in Figure 12. Patients were asymptomatic and levels returned to baseline levels by Day 29. The maximum difference in mean MetHb% was ~2.5% between the two groups at study Day 11.

Figure 12. TAF116564: Methemoglobin % change mean (SD) versus Study Visit - Safety Population



Visits #: Day of study. Visit 10: Day 1; Visit 30: Day 3; Visit 50: Day 5; Visit 60: Day 8; Visit 70: Day 11; Visit 80: Day 15;Visit 90: Day 22;Visit 100: Day 29;Visit 110: Day 60;Visit 120: day 90; Visit 130: Day 120; Visit 135: day 150;Visit 140: Day 180; Visit: 900: unscheduled visit. Visit 900: include only patients who had unscheduled visits during the study.
Source: NDA 210795, TAF116564, ADSL and ADLAB dataset, JReview 11.0

Clinical Chemistry

Both treatment groups had similar proportions of subjects with abnormal values for most chemistry parameters, and changes from baseline were similar, Table 94. Hepatic and renal parameters, and CPK results are discussed in more detail.

Table 94. TAF116564: Subjects with Abnormal Clinical Chemistry Laboratory Evaluations

Serum or Plasma Laboratory Test, n (%)	TQ+CQ (N=166)	PQ+CQ (N=85)
ALT >3xULN	8 (5)	0
AST >3xULN	6 (4)	3 (4)
Alkaline phosphatase >2.5xULN	0	1 (1)
Bilirubin >1.5xULN	28 (17)	18 (21)
Indirect bilirubin >1.5xULN	36 (22)	21 (25)
Creatine kinase >5xULN	3 (2)	4 (5)
Creatinine >3xBaseline	0	0
GFR <0.4843 mL/sec/1.73m²	0	0
Urea >11.067 mmol/L[a]	40 (24)	19 (22)

Source: Table 3.24

a. A value of 11.067 mmol/L was used as a cut-off for values of clinical concern, which was lower than the upper limit of normal for Site 207417 in Manaus, Brazil, which had an ULN of 16 mmol/L. Malaria causes a high urea via fever and dehydration, and elevations in urea were, therefore, frequently present at Baseline in all treatment groups (Source: Listing 15).

Source: NDA 210795, TAF116564, Applicant's Table 25.

Hepatic laboratory Tests

ALT post baseline elevations were higher in the TQ+CQ group than in the PQ+CQ group. Eight (2.2%) patients in the TQ+CQ arm experienced increases in ALT > 3 to ≤ 5 x ULN, six of these patients had abnormal baseline ALT values associated with *P. vivax* malaria and subsequently resolved with treatment with TQ+CQ or PQ+CQ, Table 95. No patients in the PQ+CQ group experienced ALT > 3xULN <=5xULN. There were no Hy's Law cases reported post treatment in the trial.

Table 95. TAF116564: ALT Levels Shift Tables - Safety Population

Alanine aminotransferase (ALT)	**TQ 300mg + CQ N = 166 (100%); n (%)**			**PQ + CQ N = 85 (100%); n (%)**	
ALT_Post_Base_Category	Base ALT Normal	Base ALT > ULN <=2xULN	Base ALT > 2xULN <=3xULN	Base ALT Normal	Base ALT > ULN <=2xULN
ALT Normal	70 (42.2%)	7 (4.2%)	0	37 (43.5%)	2 (2.4%)
ALT > ULN <=2xULN	37 (22.3%)	25 (15.1%)	1 (0.6%)	25 (29.4%)	11 (12.9%)
ALT > 2xULN <=3xULN	7 (4.2%)	9 (5.4%)	0	3 (3.5%)	6 (7.1%)
ALT > 3xULN <=5xULN	2 (1.2%)	5 (3.0%)	1 (0.6%)	0	0
Subjects (totals)	116 (69.9%)	46 (27.7%)	2 (1.2%)	65 (76.5%)	19 (22.4%)

Source: NDA 210795, TAF116564, ADSL and ADLAB dataset, JReview 11.0

Elevated total bilirubin levels were observed at baseline and subsequently declined to normal levels with TQ+CQ or PQ+CQ treatment as would be expected during recovery from *P. vivax* malaria. Most patients in the TQ 300mg+CQ arm had levels ≤ 2xULN, Table 96. Bilirubin levels were similar between treatment groups. One subject in the PQ+CQ group experienced Grade 2 hyperbilirubinemia on study Day 3 which resolved. One subject in the TQ+CQ group

experienced a recurrence of *P. vivax* malaria on study Day 145 and Grade 2 hyperbilirubinemia on study Day 146.

Table 96. TAF116564: Total Bilirubin - Safety Population

Total Bilirubin	TQ 300mg + CQ N = 166				PQ 15mg +CQ N=85			
Post Baseline Category	Base BILI Normal	Base BILI > ULN <=2x ULN	Base BILI > 2xULN <=3x ULN	Base BILI > 3xULN <=5x ULN	Base BILI Normal	Base BILI > ULN <=2x ULN	Base BILI > 2xULN <=3x ULN	Base BILI > 3xULN <=5x ULN
BILI Normal	65 (39.2%)	34 (20.5%)	5 (3.0%)	0	25 (29.4%)	15 (17.6%)	3 (3.5%)	0
BILI > ULN <= 2xULN	12 (7.2%)	31 (18.7%)	5 (3.0%)	2 (1.2%)	7 (8.2%)	16 (18.8%)	7 (8.2%)	2 (2.4%)
BILI > 2xULN <=3xULN	0	2 (1.2%)	5 (3.0%)	0	1 (1.2%)	3 (3.5%)	2 (2.4%)	2 (2.4%)
BILI > 3xULN <=5xULN	0	0	0 (	3 (1.8%)	0	0	0	0
BILI > 5xULN <=10xULN	0	0	0	0	0	0	1 (1.2%)	0

Source: NDA 210795, TAF116564, ADSL and ADLAB dataset, JReview 11.0

Creatine phosphokinase (CPK) or creatine kinase (CK)

Seven patients, 3(2%) in the TQ+CQ and 4(5%) in the in the PQ+CQ experienced increase in CPK levels at ≥ 5x ULN post baseline, Table 97. Postbaseline increases in CPK levels were mostly grade 1. Three subjects had elevations in CPK following intense physical exertion. One subject had an elevated CPK following phlebitis associated with an intravenous cannula. These changes resolved without specific medical intervention.

Table 97. TAF116564: Creatine phosphokinase IU/L maximum post baseline – Safety Population

Test	Baseline Grade	Maximum Grade Post Baseline	TQ 300mg + CQ	PQ + CQ
CPK Increase	Grade 0	Grade 0	115 (69.3%)	59 (69.4%)
		Grade 1 (> ULN -2.5 x ULN)	45 (27.1%)	20 (23.5%)
		Grade 2 (> 2.5 – 5 x ULN	3 (1.8%)	2 (2.4%)
		Grade 3 (> 5x ULN- 10 x ULN)	0	2 (2.4%)
	Grade 1	Grade 0	1 (0.6%)	0
		Grade 1	0	1 (1.2%)

CPK: Creatine phosphokinase.

Source: NDA 210795, TAF116564, ADSL and ADLAB dataset, JReview 11.0

Clinical reviewer's Comment: TQ and PQ have not previously been associated with rises in CPK. CQ is associated with elevated CPK and can cause myopathy with continued use; however, the patients in the trial received standard treatment doses of CQ for a total of 3 days.
Strenuous exercise, muscle trauma (contact sports, traffic accidents, intramuscular injections, surgery, convulsions, wasp or bee stings, and burns), and drugs such as cholesterol-lowering statins can damage muscle and increase serum creatine kinase (CK) concentrations. In this

study, there were no apparent renal adverse effects associated with the observed elevations in CPK levels; serum creatinine levels were not significantly raised. There were no reports of CPK elevations associated with rhabdomyolysis (urine myoglobin levels were not reported).

Cardiac Adverse Events

QTcF prolongation was observed in similar proportions of patients for both treatment groups, and < 5% of subjects in each treatment group had a ≥ 60 ms increase in QTcF or a QTcF > 480ms, Table 98. No patients had a QTcF > 500 ms.

Table 98. TAF116564: QTcF Interval (msec)

QTcF values, n (%)	TQ+CQ (N=166)	PQ+CQ (N=85)
n	166	84
≤450	117 (70)	54 (64)
>450 to ≤480	38 (23)	25 (30)
>480 to ≤500	11 (7)	5 (6)
>500	0	0
n	164	83
Increase <60	149 (91)	75 (90)
Increase ≥60 and QTcF ≤480	10 (6)	6 (7)
Increase ≥60 and QTcF >480	5 (3)	2 (2)

Source: Table 3.40

Source: NDA 210795, TAF116564, CSR, Table 27.

Renal Adverse Events

Adverse events included dysuria (n=6) and nephrolithiasis (n=2) which were not associated with study drugs. Small increases in creatinine were observed in the TQ+CQ group at Study Days 5 and 8 and stabilized over time. There were no associated changes in urea levels or glomerular filtration rate (GFR).

Clinical reviewer's comment: TQ inhibits in vitro human renal transporters OCT2, MATE1 and MATE-2K which may be associated with transient increases in creatinine observed in the trial; however, studies in vivo have not yet been performed.

Psychiatric Adverse Events

Two (1.2%) patients in the TQ+CQ arm reported insomnia. Three (3.5%) patients in the PQ+CQ arm reported anxiety, one (1.2%) patient reported depression. A 36-year-old female and the 53-year-old male complained of insomnia on study Day 6 and study Day 3, respectively. The female subject stated that the insomnia was triggered by family problems. Both patients were treated with diazepam 5 mg orally daily before bedtime for three days and the insomnia resolved in both patients after 3 to 5 days. There were no further reports of recurrence of insomnia while on study.

Clinical reviewer's comments: An association between insomnia and TQ cannot be ruled out and insomnia should be included as an adverse event in the TQ drug label. Both drugs in the regimen may be associated with insomnia because insomnia is also associated with CQ. Insomnia is a known adverse reaction associated with MQ.

Safety Evaluations in Healthy Volunteers

In the TQ development program, controlled healthy volunteer studies provided useful safety information because TQ single dose was administered without CQ which eliminates the confounding adverse events due to CQ and confounding factors due to malaria. Safety information from three healthy volunteer studies TAF110027, TAF11482 and 201807 are summarized.

Evaluation of Safety in Controlled Healthy Volunteers Studies

Study TAF110027 – Hemolytic potential of TQ

TAF110027 was a phase 1, open-label, dose-ranging study of TQ in which the hemolytic potential of TQ capsules (not the tablet) was assessed in G6PD-deficient heterozygous female healthy volunteers. All the G6PD-deficient subjects (WHO class III variant) in the trials were heterozygous females with 40-60% normal RBCs identified by enzyme activity and a cytochemical staining method which is a sensitive test for identifying heterozygous females. Additional subjects were recruited once the highest non-hemolytic dose of TQ had been defined and included adult female subjects with 61% to 80% G6PD enzyme and 81%+ G6PD enzyme to evaluate hematological safety in.

G6PD-normal female healthy volunteers were enrolled as the control with both groups receiving TQ (i.e., no placebo). A total of 51 subjects (18 to 45 years of age) were recruited i.e., 24 (47%) G6PD normal and 27 (53%) G6PD deficient adult females. All subjects in the TQ cohorts received a single dose of TQ 100mg, 200mg or 300mg as directly observed therapy (DOT). PQ 15mg daily for 14 days was the comparator.

The primary endpoint was maximum absolute decline in hemoglobin (Hgb) or hematocrit (Hct) from baseline. A Grade 2 hematology toxicity included the occurrence of any one of the following signs or symptoms Hgb decline of 1.5 g/dL (or Hct decline of 4.5%) from baseline, indirect bilirubin increase of > 50% from baseline, haptoglobin ≤ 25mg/dL, reticulocytes ≥ 4%. Dose limiting toxicity (DLT) was defined as a ≥2.5 g/dL decline in Hgb (or Hct decline of 7.5%) from baseline or any clinically significant signs and symptoms of hemolysis (e.g., pallor, jaundice, hemoglobinuria, acute renal failure, tachycardia, tachypnea, hypotension, etc.) as determined by the investigator(s). Dose escalation was stopped at TQ 300 mg, as per protocol, as three subjects experienced a DLT.

Clinical reviewer's Comment: Males with G6PD deficiency were not enrolled for safety reasons because hemizygous males carry only G6PD deficient red blood cells and are at greater risk for hemolysis and hemolytic anemia whereas heterozygous females have normal and deficient red blood cell populations.

G6PD status

The mean G6PD enzyme activity (IU/gHb) for G6PD normal and deficient cohorts are shown. G6PD-normal subjects had > 80% enzyme activity of the site median normal value. G6PD-deficient subjects had enzyme activity 40% to 60% of the site median normal value. All G6PD levels met the inclusion criteria. See Table 99.

Table 99. TAF110027: G6PD Status

Cohort	G6PD Status	N[a]	G6PD Enzyme Activity, Mean (IU/gHb)	SD (IU/gHb)	G6PD Enzyme Activity, Median (IU/gHb)	Minimum (IU/gHb)	Maximum (IU/gHb)
A1 TQ 100mg	Normal	6	13.22	7.77	11.96	4.44	23.3
	Deficient	6	3.62	1.47	3.51	2.18	5.76
A2 TQ 200mg	Normal	6	12.16	1.01	12.07	10.87	13.63
	Deficient	6	6.21	0.21	6.18	5.96	6.55
A3 TQ 300mg	Normal	6	13.75	2.91	12.61	11.08	18.80
	Deficient	3	5.85	0.98	6.24	4.73	6.57
A6 TQ 200mg[b]	Deficient	2	7.92	1.01	7.92	7.20	8.63
A7 TQ 200mg[c]	Deficient	5	10.22	1.05	9.81	9.52	12.09
A8 PQ 15mg	Normal	6	12.47	0.85	12.48	11.35	13.66
	Deficient	5	5.66	0.69	5.51	5.03	6.67
Cohort	**G6PD Status**	**n**	**G6PD Enzyme Activity, Mean (%)**	**SD (%)**	**G6PD Enzyme Activity, Median (%)**	**Minimum (%)**	**Maximum (%)**
A1 TQ 100mg	Normal	6	114.6	67.4	103.6	38.5	201.9
	Deficient	6	31.4	12.7	30.4	18.9	49.9
A2 TQ 200mg	Normal	6	105.4	8.7	104.6	94.2	118.1
	Deficient	6	53.8	1.8	53.6	51.6	56.8
A3 TQ 300mg	Normal	6	119.1	25.2	109.3	96.0	162.9
	Deficient	3	50.7	8.5	54.1	41.0	56.9
A6 TQ 200mg	Deficient	2	68.6	8.8	68.6	62.4	74.8
A7 TQ 200mg	Deficient	5	88.6	9.1	85.0	82.5	104.8
A8 PQ 15mg	Normal	6	108.0	7.4	108.1	98.4	118.4
	Deficient	5	49.0	5.9	47.7	43.6	57.8

Data Source: Table 10.4

a. n=N

b. G6PD enzyme activity 61% to 80% of the site median normal value

c. G6PD enzyme activity 81%+ of the site median normal value

Note: Cohorts A6 and A7 were recruited in parallel, with a maximum of 3 subjects dosed from each cohort at one time.

Source: NDA 210795, TAF110027 CSR, Applicant's Table 10.4.

Adverse Events

There were no deaths or serious adverse events reported in TAF110027, (N=51). All AEs were mild in severity. No gastrointestinal adverse reactions were reported; TQ was administered after a meal. Hgb decreases was the mostly frequently reported adverse event, reported in 4, 3, and 2 subjects in the TQ 100mg, TQ 300mg, and PQ 15mg treatment groups, respectively, Table 100. In the TQ groups, dizziness and headache were reported in two subjects each and one subject had an elevated ALT (~1.5 x ULN). Dizziness which appeared to be related to TQ at all doses tested. All cases of dizziness were mild and of short duration. One case of elevated hepatic transaminases [ALT (59 IU/L) and AST (66 IU/L)] in a G6PD-deficient subject with normal baseline values who received TQ 200 mg was attributed to TQ. TQ had a similar safety profile (decline in Hgb, increases in MetHb% and dizziness) to PQ. No significant effects of any dose of TQ or PQ on QT interval (corrected or uncorrected) or QRS duration were reported.

Table 100. TAF110027: Treatment Emergent Adverse Events in Healthy Volunteers by Treatment Arm

Preferred Term	TQ 100 mg single dose N = 11	TQ 200 mg single dose N =12	TQ 300 mg single dose N = 19	PQ 15mg daily for 14 days N = 9
Hemoglobin decreased	4 (36.3%)	0	3 (15.8%)	2 (22.2%)
Nasopharyngitis	3 (27.2%)	0	0	0
Hematocrit decreased	0	1 (8.3%)	0	1 (11.1%)
Dizziness	1 (9.0%)	1 (8.3%)	0	0
Headache	2 (18.1%)	0	0	0
Alanine aminotransferase increased	0	1 (8.3%)	0	0
Aspartate aminotransferase increased	0	1 (8.3%)	0	0
Rhinorrhea	1 (9%)	0	0	0
Pyrexia	1 (9%)	0	0	0
Nausea	1 (9%)	0	0	0
Myalgia	1 (9%)	0	0	0

Source: NDA210795, TAF110027, AE dataset, JReview v.12.2

Clinical reviewer's Comment: Pruritus was relatively common in the TQ+CQ trials but was rarely reported in healthy volunteer studies of TQ administered without CQ.

In the G6PD-deficient cohort (n=27), there were more subjects with declines of Hgb who received TQ 300mg single-dose as compared to TQ < 300mg and to G6PD-normal controls; however, the number of subjects was small and the study was not powered to conduct any formal comparison, Table 101.

Table 101. TAF110027: Selected Treatment Emergent Adverse Events in G6PD-deficient Patients

System Organ Class	Preferred Term	PQ 15mg N=5	TQ 100mg N=6	TQ 200mg N=13	TQ 300mg N=3
Investigations	ALT Increased	0	0	1 (8%)	0
	AST Increased	0	0	1 (8%)	0
	Hematocrit Decrease	1 (20%)	0	1 (8%)	0
	Hemoglobin Decrease	2 (40%)	1 (17%)	0	3 (100%)
	MetHb % increase ≥ 5%	0	0	2 (16%)	1 (33%)
Nervous System Disorders	Dizziness	0	1 (17%)	1 (8%)	0
	Headache	0	1 (17%)	0	0

Source: NDA210795, TAF110027, AE dataset, JReview v.12.0

Patients with hematologic toxicities are summarized in Table 102. Three G6PD deficient patients in the TQ 300mg group experienced dose limiting toxicities and dose escalation was therefore stopped at 300mg.

Table 102. TAF110027: Hematological Toxicities at any Study Visit

Cohort	G6PD Status	N	Haematological Toxicity[a]	Dose Limiting Toxicity
A1 TQ 100mg	Normal	6	4	0
	Deficient	6	6	0
A2 TQ 200mg	Normal	6	5	0
	Deficient	6	6	2
A3 TQ 300mg	Normal	6	0	0
	Deficient	3	3	3
A6 TQ 200mg	Deficient	2	1	0
A7 TQ 200mg	Deficient	5	3	0
A8 PQ 15mg	Normal	6	6	0
	Deficient	5	4	3

Data Source: Table 10.6

a. Grade 2 or above, defined as Hb decline of 1.5 g/dL(or Hct decline of 4.5%) from baseline, indirect bilirubin increase of >50% from baseline, haptoglobin ≤25 mg/dL, reticulocytes ≥4%, and other clinically significant signs and symptoms as judged by the investigator

Cohorts A6 and A7: These G6PD deficient cohorts were recruited in parallel, with a maximum of 3 subjects dosed from each cohort at one time.
Source: Source: NDA210795, TAF110027 CSR, Applicant's Table 10.6.

Hemoglobin decreases on treatment

Declines in hemoglobin were seen in G6PD normal subjects (n=24); Hgb decrease of > 2g/dl was reported in one subject in the TQ 200mg group, (Table 103). There were no Hgb declines of ≥ 3g/dL.

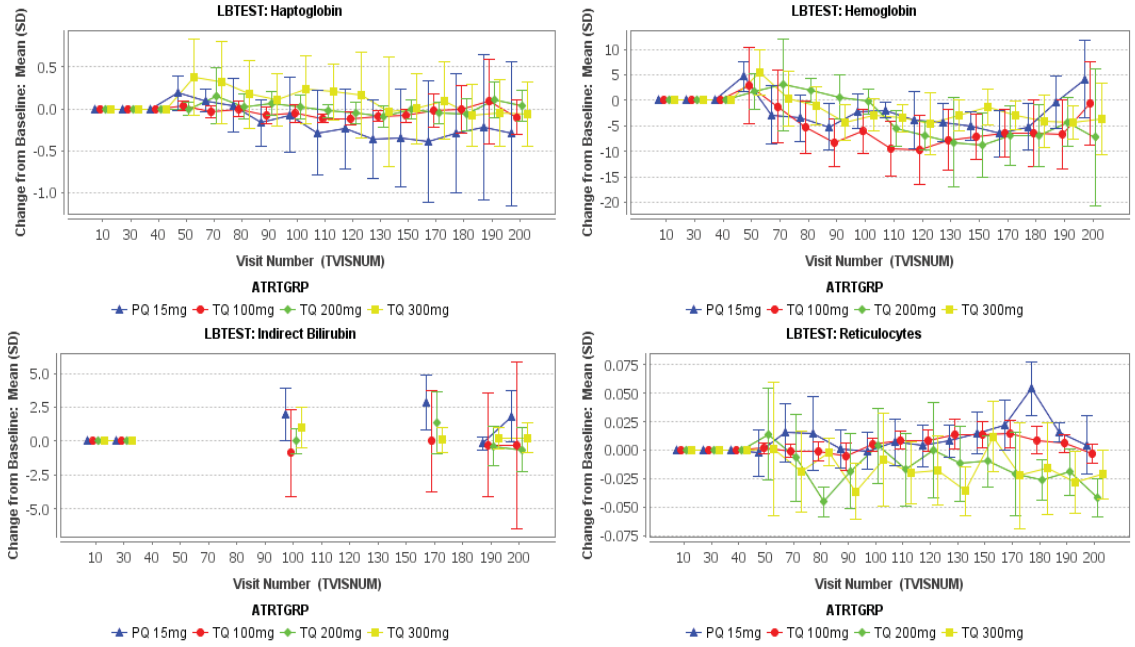
Table 103. TAF110027: Hemoglobin(Hgb) g/dL Decrease from Baseline – G6PD Normal Subjects, N=24

Hgb Decrease (g/dL)	PQ 15mg N=6	TQ 100mg N=6	TQ 200mg N=6	TQ 300 mg N=6
> 1.0 to ≤ 2.0	4 (66.6%)	5 (83.3%)	4(66.6%)	3 (50%)
> 2.0	0	0	1(17%)	0

Source: NDA210795, TAF110027, Lab dataset, JReview v.12.0

The proportion of patients with decreases in mean Hgb from baseline were greater in the TQ 100 mg group than other dose groups. Mean reticulocyte count increases were higher in the PQ and TQ 100mg groups than in the other TQ groups. Mean haptoglobin levels declined in the PQ 15mg group but the declines were minimal in the TQ groups. Mean indirect bilirubin levels were elevated in PQ groups and the TQ 300 mg around study Day 7 (visit # 100). Changes from baseline were small for all laboratory parameters. There was no laboratory evidence of significant hemolysis in any treatment group. See Figure 13.

Figure 13. TAF 110027: Changes in Mean (+/- SD) Hemoglobin g/L, Reticulocytes 10^{12}/µl, Bilirubin µmol/L, Haptoglobin mg/dL from Baseline by Study Visit – G6PD-normal subjects



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

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

In G6PD-deficient subjects (n=27), the greatest decline (3.1 g/dL) in Hgb was observed in a subject with 40-60% G6PD enzyme activity who received TQ 200mg. A decrease in Hgb of > 2g/dL was observed in seven subjects in the TQ groups and four subjects in the PQ group. One subject in the TQ 200mg group had decrease in Hgb ≥3g/dL, (Table 104).

Table 104. TAF110027: Hemoglobin(Hgb) g/dL decrease from baseline in G6PD deficient volunteers, N=27.

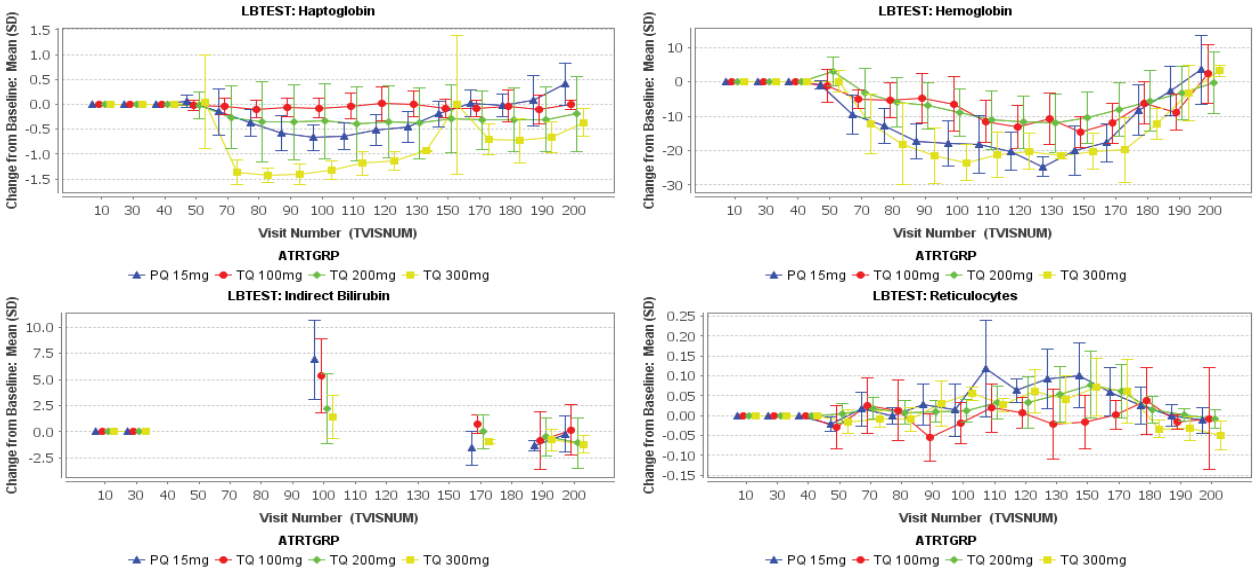
Hgb Decrease (g/dL)	PQ 15mg N=5	TQ 100mg N=6	TQ 200mg N=13[a]	TQ 300mg N=3
>1.0 to ≤ 2.0	1 (20%)	3 (50.0%)	9 (69%)	0
> 2.0 to ≤ 3.0	4 (80%)	2 (33.3%)	1 (8%)	3 (100.0%)
> 3.0	0	0	1 (8%)	0

One subject (PQ 15 mg) withdrew consent for personal reasons on Day 6.
[a] Includes 7 patients with 61% to 80% G6PD enzyme (n=2) and 81%+ G6PD enzyme (n=5) to evaluate hematological safety in heterozygous females with >60%.
Source: NDA 210795, TAF110027, Laboratory dataset, JReview v.12.0

The proportion of patients with mean Hgb decreases were dose-dependent, i.e., greater in TQ 300 mg group (and PQ group) than with lower TQ doses and all recovered without medical intervention. Mean reticulocyte count increases were higher in the TQ 300 mg group and PQ groups in the G6PD-deficient cohort than in the G6PD-normal cohort. Mean haptoglobin levels

declined from baseline in the TQ 300 mg and PQ groups. Mean indirect bilirubin levels were increased around Day 7 (visit # 100) and were more pronounced in the TQ 100 mg and PQ groups. Subjects recovered without medical intervention. The laboratory results were consistent with mild hemolysis. See Figure 14.

Figure 14. TAF 110027: Changes in Mean (SD) Hemoglobin g/L, Reticulocytes 10^{12}/µL, Bilirubin umol/L, and Haptoglobin mg/dL from Baseline by Study Visit – G6PD-deficient subjects



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

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

Clinical Reviewer's Comment: In study TAF110027, TQ single dose was associated with declines in Hgb in G6PD-normal healthy individuals. A greater proportion of subjects experienced declines of Hgb within the G6PD-deficient cohort who received TQ 300 mg as compared to the lower doses and to G6PD-normal controls; however, numbers of subjects were small and not powered to conduct a formal comparison.

<u>Haptoglobin</u>

Haptoglobin levels were reduced (indicator of hemolysis) in the TQ 300 mg and PQ groups, as compared to their control arm, in G6PD deficient individuals, Table 105.

Table 105. TAF110027: Maximum Change from Baseline in Haptoglobin (g/L) - Safety Population

Cohort	G6PD Status	N	n	Mean (g/L)	SD (g/L)	Median (g/L)	Minimum (g/L)	Maximum (g/L)
A1 TQ 100mg	Normal	6	6	-0.22	0.10	-0.24	-0.34	-0.08
	Deficient	6	6	-0.23	0.21	-0.19	-0.61	-0.05
A2 TQ 200mg	Normal	6	6	-0.18	0.11	-0.17	-0.35	-0.06
	Deficient	6	6	-0.50	0.42	-0.37	-1.14	-0.08
A3 TQ 300mg	Normal	6	6	-0.43	0.49	-0.45	-1.15	0.37
	Deficient	3	3	-1.43	0.15	-1.52	-1.52	-1.25
A6 TQ 200mg	Deficient	2	2	-0.39	0.06	-0.39	-0.43	-0.35
A7 TQ 200mg	Deficient	5	5	-0.84	1.08	-0.34	-2.74	-0.18
A8 PQ 15mg	Normal	6	6	-0.55	0.72	-0.30	-2.00	-0.14
	Deficient	5	5	-0.65	0.24	-0.62	-1.04	-0.39

Data Source: Table 10.5

Note: Cohorts A6 and A7: These cohorts of G6PD deficient subjects were recruited in parallel, with a maximum of 3 subjects dosed from each cohort at one time. Haptoglobin approximate normal range: 3-20g/L.
Source: NDA 210795, TAF110027, Applicant's Table 10.5

Methemoglobinemia

Methemoglobin levels and max increase in MetHb% from baseline are summarized G6PD deficient patients and G6PD normal subjects in Table 106. Three G6PD deficient patients in the TQ-treated group had a methemoglobin levels > 5%, (normal is < 3%). One patient (G6PD normal) in the PQ group had a MetHb increase to >10%. No subject was reported to have clinical signs or symptoms of methemoglobinemia.

Table 106. TAF110027: Methemoglobin% max value and max change from baseline

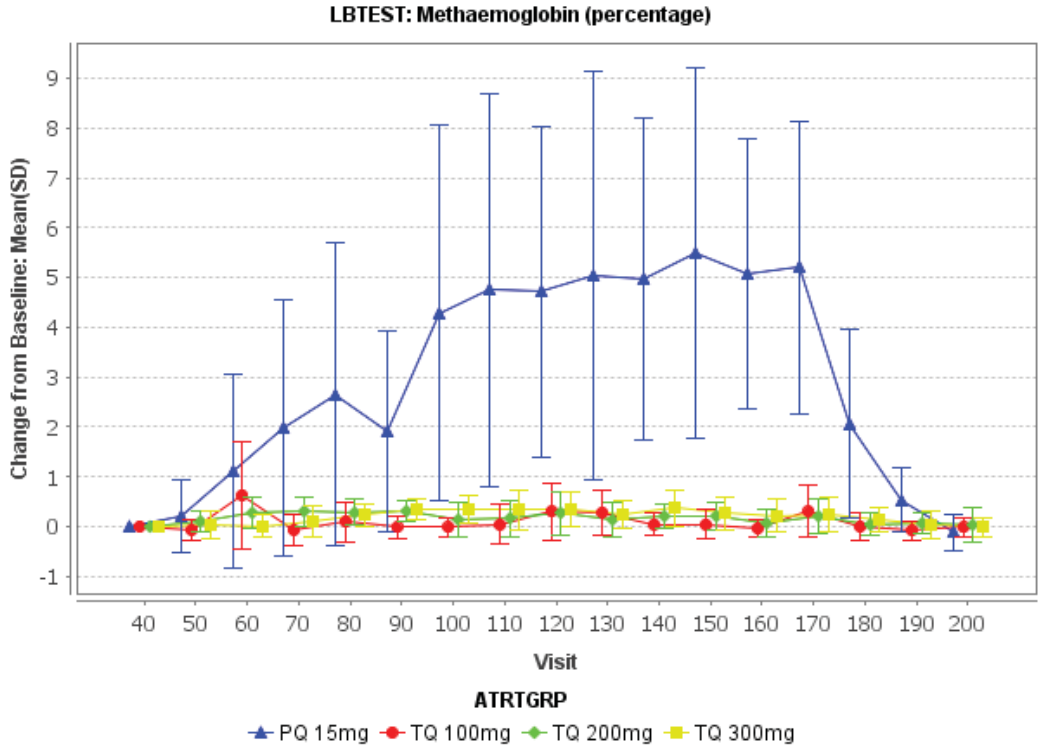
	Methemoglobin	TQ 100mg [n (%)]	TQ 200mg [n (%)]	TQ 300mg [n (%)]	PQ 15mg x 14 days [n (%)]
G6PD deficient					
Methemoglobin (%) maximum	Methemoglobin ≥ 1%	6 (100)	13 (100)	3 (100)	5 (100)
	Methemoglobin ≥ 2%	2 (33.3)	5 (38.5)	2 (66.7)	4 (80)
	Methemoglobin ≥ 3%	2 (33.3)	2 (15.4)	1 (33.3)	2 (40)
	Methemoglobin ≥ 5%	0	2 (15.4)	1 (33.3)	0
Methemoglobin % Change from baseline	increase Methemoglobin ≥ 1%	3 (50)	2 (15.4)	3 (100.0)	3 (60)
	increase Methemoglobin ≥ 2%	2 (33.3)	2 (15.4)	1 (33.3)	2 (40)
	increase Methemoglobin ≥ 3%	0	2 (15.4)	1 (33.3)	0
	1stColItemSubjects	6 (100)	13 (100)	3 (100)	5 (100)
G6PD normal					
Methemoglobin %	Methemoglobin ≥ 1%	6 (100)	6 (100)	6 (100)	6 (100)
	Methemoglobin ≥ 2%	2 (33.3)	0	3 (50)	6 (100)
	Methemoglobin ≥ 3%	1 (16.7)	0	0	6 (100)
	Methemoglobin ≥ 5%	0	0	0	4 (66.7)
	Methemoglobin >=10%	0	0	0	1 (16.7)

	Methemoglobin	TQ 100mg [n (%)]	TQ 200mg [n (%)]	TQ 300mg [n (%)]	PQ 15mg x 14 days [n (%)]
Methemoglobin % Change from baseline	increase Methemoglobin ≥ 1%	3 (50.0)	1 (6.7)	1 (16.7)	6 (100)
	increase Methemoglobin ≥ 2%	1 (16.7)	0	0	5 (83.3)
	increase Methemoglobin ≥ 3%	0	0	0	5 (83.3)
	increase Methemoglobin ≥ 5%	0	0	0	3 (50)
	increase Methemoglobin ≥ 10%	0	0	0	1 (16.7)
	1stCollItemSubjects	6 (100)	6 (100)	6 (100.0)	6 (100)

Source: NDA 210795, TAF110027, Laboratory dataset, JReview v.12.0

PQ 15 mg daily was associated with larger increases in mean MetHb% than any dose of TQ (50mg to 600mg) in subjects in the G6PD-normal cohort, (Figure 15).

Figure 15. TAF110027: Maximum change mean (SD) methemoglobin % by visit - G6PD normal



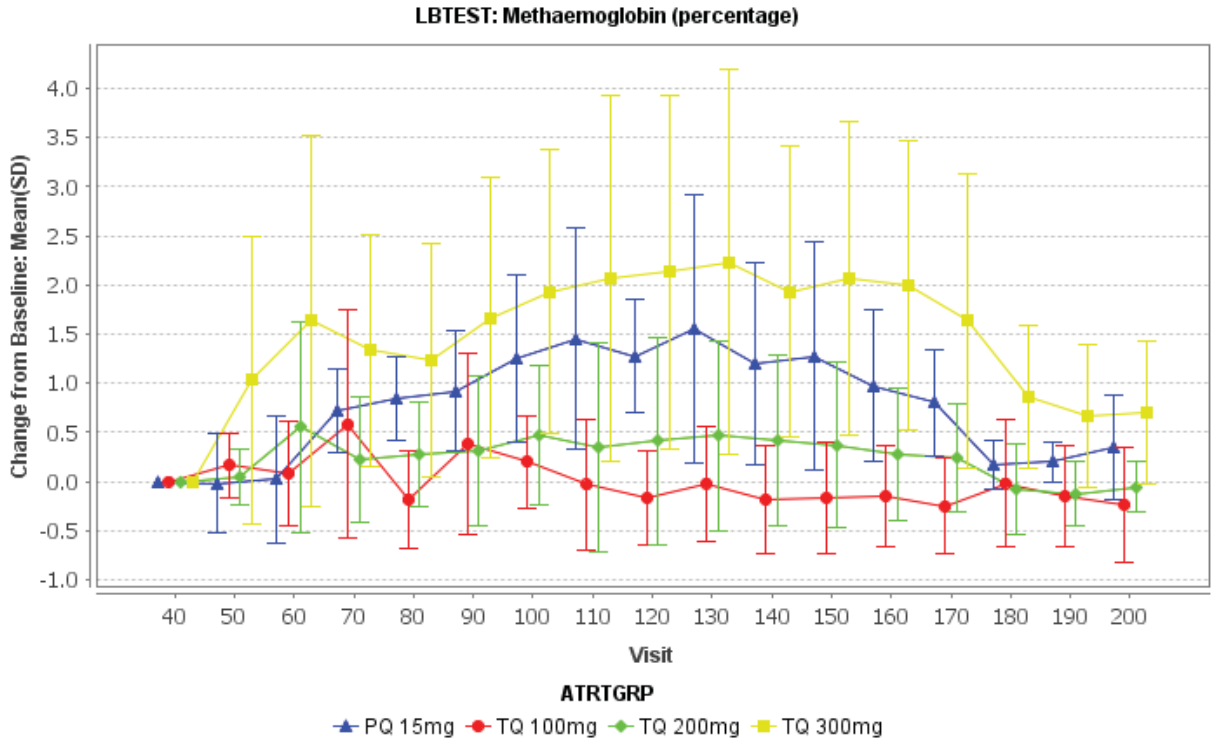
G6PD normal population

SD: Standard deviation

Source: NDA 210795, TAF110027, Demographic and Laboratory datasets, JReview 12.0

In G6PD-deficient subjects, TQ caused small increases in MetHb% across study visits with a maximum increase of 4.5% in TQ 300 mg group. The increases in MetHb% in the TQ arms were dose-dependent. Interestingly, the maximum mean increases in MetHb% across study visits were higher in the TQ 300mg group than the PQ group, (Figure 16).

Figure 16. TAF110027: Maximum change mean (SD) methemoglobin % by visit - G6PD deficient



G6PD deficient population

Source: NDA 210795, TAF110027, Demographic and Laboratory datasets, JReview 12.0

To further support the proposed contraindication in G6PD deficiency in the TQ label, the Applicant noted that in a phase 1 study that closed due to poor enrollment, there were two cases of hemolytic anemia with TQ 1200 mg (total dose) when administered inappropriately to two G6PD-deficient (WHO class III) female healthy volunteers (one heterozygous and one homozygous) in a *P. vivax* prophylaxis study. One subject had a Hgb decline of 37% from baseline with clinical signs of hemolysis and the other subject had a Hgb decline of 25%. In addition, two G6PD-deficient heterozygous female carriers in a TQ and CQ (CQ) drug-drug interaction study, who each received 2 x 450 mg doses of TQ, experienced a total Hgb decline of 2.8 g/dL and 3 g/dL from baseline, respectively.

Clinical Reviewer's Comment: The clinical reviewer agrees with the applicant that TQ should be contraindicated in G6PD-deficient subjects with enzyme activity level < 70% or a patient with unknown status because of the risk of hemolysis, hemolytic anemia, and methemoglobinemia. Similar adverse reactions are associated with PQ. G6PD testing should be done prior to starting TQ.

Study TAF114582

Study TAF114582 was a placebo-controlled Thorough QT study which enrolled 260 healthy volunteers who were G6PD normal. This study was designed to compare the effects of TQ mono-therapy (300mg, 600mg or 1200mg), over three consecutive days, on the changes in QT duration to those observed in subjects dosed with moxifloxacin or placebo. This was a randomized, single-blind, placebo controlled, parallel group study. Moxifloxacin was used as a

positive control to validate the sensitivity of the study in detecting changes in QTc interval prolongation.

All AEs were mild or moderate in intensity, except for two cases of hypersensitivity and one severe AE of increase in serum creatine phosphokinase (CPK), (Table 108).

Disposition

The disposition subject is summarized in Table 107. Five subjects were lost follow up. Two subjects withdrew consent. One subject in the TQ 1,200 mg treatment group withdrew from the study after the first dose of TQ 400 mg because of nausea and vomiting which resolved within 24 hours.

Table 107. TAF114582: Disposition

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

Serious Adverse Events

There were no deaths. Two cases of hypersensitivity were reported with an onset 13 to 15 days after TQ administration. Symptoms and signs reported included angioedema and diffuse urticaria. The delay in onset of the events post treatment and the duration of symptoms were not consistent with anaphylaxis. The subjects recovered following with treatment with prednisone and diphenhydramine. The two cases of hypersensitivity are described in TAF114582 and in section, 9.1.4.

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

The elevations in CPK levels observed in two patients and elevations in CPK and AST in one patient were associated with muscle injury due to strenuous physical exercise.

Table 108. TAF114582: Serious Adverse Events

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

Preferred Term	Placebo N = 52	Moxifloxacin N = 52	TQ 300mg N = 52	TQ 600mg N = 52	TQ 1200mg N = 52
Urticaria	0	0	1 (1.9%)	0	0

Source: NDA 210795, TAF114582, Lab dataset, JReview v.12.0

Decrease in Hemoglobin

Decrease in hemoglobin > 2.5g/dL was reported for one subject in the TQ 600mg group and there were no reports in the TQ 300mg or TQ 1,200mg groups.

Subject (b) (6) (TQ 600 mg), a 36-year-old male, had a drop in Hgb to 13.3 g/dL (a drop of >2.5 g/dL from baseline of 16 g/dL) on Day 6. No evidence of hemolysis was noted (no schistocytes, haptoglobin normal, total bilirubin normal, direct & indirect bilirubin normal, LDH normal, Direct Coombs negative). Repeat Hgb was 15.6g/dL on Day 12. The subject has no relevant medical history or concomitant medications. He remained in the study and the event resolved without medical intervention within five days.

Clinical reviewer's comment: This was no evidence of hemolysis associated with the decrease in Hgb levels. There was no report of blood loss. Rehydration may have been a contributing factor to some of the decline in Hgb levels. However, the decrease in Hgb could be related to TQ because of its temporal association.

Increase in creatine phosphokinase (CPK) levels.

Increases in CPK levels was reported in three subjects.

Subject (b) (6) (TQ 600 mg), a 46-year-old male, elevations in CPK >7000 IU/L and concurrent increase in ALT=126 (ALT 3x ULN), AST= 227 (AST 6x ULN) at 26 days after starting study drugs. The patient did not follow the protocol restrictions on exercise (weight training) and to taking protein supplements and energy drinks. He remained asymptomatic and discontinued supplements two days later. Seven days after stopping supplements, ALT/AST and CPK were in the normal range. Creatinine was 1.15 mg/dL and blood urea nitrogen (BUN) was 12 mg/dL. Hemoglobin, haptoglobin, and troponin remained within normal levels throughout.

Subject (b) (6) (TQ 600 mg), a 29-year-old male, experienced developed increased levels of CPK >7000 IU/L (*normal range: 39 - 308 U/L*) on Day 7 (i.e., five days after the last dose of study drugs) with concurrent rise in AST to 7x ULN on Day 8. There was no confounding medical history or concomitant medications. The subject admitted to not following study restrictions for physical activity (did weight training). CPK declined rapidly from 7000 to 1053. AST returned to normal. ALT remained normal throughout. Subject remained asymptomatic during the study. The adverse event resolved without specific medical intervention in 6 days.

Subject (b) (6) (placebo), a 27-year-old male, experienced severely (grade 4) elevated creatine phosphokinase (15, 314 IU/L, normal range 49 - 397) on Day 25 after the start of investigational drugs. The patient admitted to have undertaken strenuous exercise against protocol

requirements. Concomitant medications included hydrocortisone. The subject remained in the study and the adverse event resolved within 56 days.

Treatment Emergent Adverse Events

Adverse events occurring in more than 3% of subjects in the TQ 300mg group included, nausea, vomiting, diarrhea, abdominal pain, headache, dizziness, and upper respiratory tract infections, (Table 109).

Gastrointestinal adverse effects were the most commonly reported adverse events. The frequency of nausea increased from 10% to 33% as the dose of TQ increased from TQ 300mg to 1,200mg indicating that TQ is associated with nausea.

Contact dermatitis / application site dermatitis was due to irritation caused by ECG skin electrodes and was reported in all treatment arms and was not related to study drugs.

Dizziness occurred in zero subjects in the placebo group, 3 (6%) subjects in the moxifloxacin group, 2 (4%) subjects in the TQ 300 mg group, 2(4%), subjects in the TQ 600 mg group, and 2(4%) subjects in the TQ 1200 mg group. Dizziness appeared to be related to study drugs. All cases of dizziness were mild, of short duration, and resolved.

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

Table 109. TAF114582: Select Treatment Emergent Adverse Events occurring in Healthy Volunteers

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

Source: NDA 210795, TAF114582, AE dataset, JReview v.12.0

QTc interval

TQ 400mg daily for 3 days (total =1,200mg), which was four times the therapeutic exposures, did not prolong the QTc interval to any clinically relevant extent. No clinically significant changes in vital signs or ECGs were observed. See section 9.1.4 for the QT-IRT team's assessment.

Laboratory Assessments

Hematology

No patient experienced Hgb drop > 3g/dL from baseline which was a predefined SAE in the placebo-controlled trials. Hgb decreases >2 g/dL occurred in all treatment groups including the placebo and moxifloxacin treatment groups. These drops in Hgb were not considered clinically significant. Hgb decreases from baseline in the TQ300mg group were the same as placebo, Table 110. Hgb levels returned to baseline levels by the final follow up visit.

Table 110. TAF114582: Decreases in Hemoglobin levels – Safety population

Hgb Decrease Category	Placebo N=52 n(%)	Moxi N=52 n(%)	TQ 300mg N=52 n(%)	TQ 600mg N=52 n(%)	TQ 1200mg N=52 n(%)
>1 to ≤2 g/dL	16 (31)	18 (35)	16 (31)	19 (37)	18 (35)
>2 to ≤3 g/dL	2 (4)	3 (6)	2 (4)	4 (8)	4(8)
>3 g/dL	0	0	0	0	0

Source: NDA 210795, TAF114582, laboratory dataset, JReview v. 12.0

Clinical reviewer's Comment: The proportion of patients experiencing decreases in Hgb in patients who received TQ 300mg were similar to the placebo. However, the applicant's analysis noted a dose relationship, with TQ 300 mg causing a mild (approximately 0.4 g/dL) decreases from baseline in hemoglobin and 1,200 mg causing approximately 1 g/dL decreases when compared to placebo; maximal effects were seen at study Day 27.

Methemoglobin

Dose-related increases in MetHb% were observed in subjects receiving single-doses of TQ 300 mg, 600 mg and 1,200 mg, (Table 111). Two (4%) patients in the TQ 300mg group and 16 (31%) patients in the TQ 1200mg group had MetHb% 3x to 5x ULN. Patients were asymptomatic and all MetHb% levels returned to normal by the final follow up visit (Day 60 post dose).

Table 111. TAF114582: Methemoglobin levels by treatment arm

Laboratory Test	MetHb% Category	Placebo N-52	Moxi N-52	TQ 300mg N=52	TQ 600mg N=52	TQ 1200mg N=52
Methemoglobin%	<1	20 (38.5%)	18 (34.6%)	15 (28.9%)	4 (7.7%)	1 (1.9%)
	>=1.0 <2.0	31 (59.6%)	33 (63.5%)	32 (61.5%)	25 (48.1%)	6 (11.5%)
	>=2.0 <3.0	1 (1.9%)	0	3 (5.8%)	14 (26.9%)	6 (11.5%)

Laboratory Test	MetHb% Category	Placebo N-52	Moxi N-52	TQ 300mg N=52	TQ 600mg N=52	TQ 1200mg N=52
	>=3.0 <5.0	0	0	2 (3.9%)	7 (13.5%)	20 (38.5%)
	>=5.0 <10.0	0	0	0	2 (3.9%)	16 (30.8%)
	>10.0	0	1(1.9%)	0	0	3 (5.8%

Moxi: moxifloxacin
MetHb% < 3% is considered normal.
Source: NDA 210795, TAF114582, laboratory dataset, JReview v.12.0

Liver function tests

Five subjects treated with TQ had increases in ALT or AST that were > 3 to 7 x ULN: two subjects in the TQ 600 mg group, and two subjects in the TQ 1200 mg group, Table 112. No subject in the TQ 300 mg group experienced elevations in ALT >3 x ULN. No dose-related increases were observed.

Three subjects (Subjects (b) (6)) in the TQ 600 mg group had ALT and/or AST elevations reported as AEs or SAEs. No subject had an increase in total bilirubin > 2 x ULN. Two of these patients ((b) (6)) had concomitant elevations in CPK levels and are discussed under CPK elevations.

Subject (b) (6) (36y male) had an increase in ALT 5x ULN that peaked at Day 8 (5 days after last TQ dose) and resolved by Day 60. ALT was normal at baseline. This subject also experienced a Hgb decrease > 2.5 g/dL at Day 8, (baseline Hgb 16.0 g/dL; Day 8 Hgb 13.3 g/dL). A repeat Hgb level was 15.6g/dL five days later. No evidence of hemolysis was found and the subject was asymptomatic. Blood smear tests were normal with no evidence of schistocytes. Serum haptoglobin levels remained normal. Indirect bilirubin and LDH levels were also normal.
Clinical reviewer's Comment: Elevations in AST levels are probably related to muscle injury in this case.

In the TQ 1200 mg group, Subjects (b) (6) and (b) (6) experienced increases in ALT that were > 3 x ULN:
Subject (b) (6) had an ALT level 3x ULN and viral serology results that indicated possible recent or concurrent Epstein-Barr virus (EBV) infection, although the EBV serology was inconclusive. ALT was within the normal range at baseline. The exposure to TQ was higher than the mean Cmax; mean Cmax for this subject was 902 ng/mL (overall mean was 724 ng/mL), AUC(0-t) was 49850 ng.h/mL (overall mean was 41896ng.h/mL), and Tmax was 15.1 hours (overall mean was 12 hours). No definitive cause for the ALT elevations was reported.

Subject (b) (6) had slightly elevated ALT at baseline (59 IU/L; > ULN). This subject experienced an ALT increase that was 4x ULN on Day 8, which resolved on Day 20. However, the subject's ALT remained outside the normal range throughout the study. The subject reported no recent travel, herbal medication, other concomitant medications, alcohol ingestion. Mean Cmax for this subject was 700 ng/mL (overall mean was 724 ng/mL), AUC(0-t) was 39269 ng.h/mL (overall mean was 41896ng.h/mL), and Tmax was 12 hours (overall mean was 12 hours). No definitive cause for the ALT elevations was reported.

Table 112. TAF114582: Subjects with elevated hepatic transaminases

Subject (b) (6)	Treatment	Lab test (units)	Visit	Study Day	Value	Normal Range	Fold ULN Value
	Placebo	AST (IU/L)	27 Day FU	26	615	3 - 34	15.000
	TQ 600 mg	AST (IU/L)	8 Day FU	8	249	3 - 34	7.3235
	TQ 600 mg	ALT (IU/L)	8 Day FU	8	212	15 - 41	5.1707
	TQ 600 mg	ALT (IU/L)	27 Day FU	27	126	15 - 41	3.0732
		AST (IU/L)	27 Day FU	27	227	3 - 34	6.6765
	TQ 1200 mg	ALT (IU/L)	Day 6	6	136	15 - 41	3.3171
	TQ 1200 mg	ALT (IU/L)	8 Day FU	8	173	15 - 41	4.2195

FU=Follow-up, Unsched=Unscheduled
Source Data: Table 10.19

Source: NDA 210795, TAF114582, Applicant's Table 10.19

In summary, TQ doses >300mg may be associated with transient elevations in hepatic transaminases. No increases >3 x ULN were observed in the TQ 300 mg or the moxifloxacin groups.

Renal Function

Serum creatinine levels were transiently raised across all treatment groups, Table 113. No patient experienced a rise in serum creatinine > 1.5 x ULN. Overall, adverse events in the TQT trial were similar to those reported in the phase 2b/3 clinical trials.

Table 113. TAF114582: Subjects with elevated creatinine levels

Test	Placebo N=52	Moxifloxacin N = 52	TQ 300mg N=52	TQ 600mg N=52	TQ 1200mg N=52
Serum Creatinine > ULN	1 (2%)	4 (8%)	3 (6%)	12 (23%)	6 (12%)

Source: NDA 114582, CSR, adapted from Table 10.46

Study 201807 - Ophthalmologic safety study

Study 201807 was a phase 1, multi-center, single-masked, randomized, placebo-controlled, parallel-group study to investigate the ophthalmologic safety and pharmacodynamics of TQ 300mg single dose in adult male and female healthy volunteers, 17 to 43 years of age.
A total of 330 subjects received TQ 300mg single-dose and 168 received placebo (information from 120-day safety update). There were no deaths or SAEs in the study.
No retinal toxicity or other ophthalmologic adverse effects were found.
Headache (23 subjects, 7%) and nausea (14 subjects, 4%), the most common AEs reported, were more frequent in the TQ 300 mg group as compared to placebo. Nervous system AEs of dizziness, somnolence, and dysgeusia were reported in the TQ group (2 subjects, <1% each), but not the placebo group. There were no reports of decreases in Hgb levels in the study.

Clinical reviewer's comment: *The ophthalmologic tests of the retina performed in study 201807 were more comprehensive than any study in the TQ development program. Subjects with any baseline retinal abnormality were excluded from the study which was not the case in other studies. The DTOP reviewer concluded that the study results from Study 201807 in healthy subjects do not indicate any clinically significant ocular risk from the use of TQ 300mg single-*

dose treatment. There are no labeling recommendations from DTOP. See ophthalmologic consult review (5/11/2018) by William Boyd, M.D. in DARRTS.

Psychiatric Adverse Effects in Healthy Volunteer Studies
Psychiatric effects were reported in six healthy subjects across the development program. Three of the patients did not have a history of psychiatric illness. All patients received TQ single doses > 300mg or multiple doses.

Single-dose TQ studies: In the TQ development program, a healthy volunteer study 050 (not reviewed in this document), reported psychosis in two subjects, one received single dose TQ 350 mg single-dose and the second patient received TQ 500 mg single-dose. The subject who received TQ 350mg single-dose had two previous episodes of psychosis and the second patient had a recent diagnosis of schizophrenia. The patients did not disclose their psychiatric history at screening. Both patients were hospitalized and recovered. One healthy volunteer without a medical history of depression received TQ 600mg single-dose and developed a depressed mood on Day 4 which resolved after 3 days and was probably related to study drug; this case is described under study TAF114582 in this review. An additional case of depression mood was reported in a patient with *P. vivax* malaria who received TQ 600 mg + CQ in Study TAF112582 part 1; the patient had a history of depression and diazepam use.

Multiple-dose TQ studies: In study 057, multiple dose study (not reviewed in this document), one subject who received cumulative doses TQ 1,600mg, developed depression at Day 37 and recovered in 15 days. Another patient who received cumulative doses 5,200mg was diagnosed with bipolar depression at 62 days post dosing and the adverse event was ongoing at the time of the study completion; it is unclear if this adverse event was related to TQ. In study 014, multiple dose study (not reviewed in this document) one patient, who received a cumulative TQ 1,200mg dose, developed hallucinotic psychosis on Day 27 and was hospitalized and the event was reported as not resolved; the patient had an undisclosed history of hallucinotic psychosis six months prior to study enrollment.

Clinical reviewer's comment: The risk of developing a psychiatric adverse event (other than insomnia) is low with a single dose of TQ 300mg. However, it would be appropriate to avoid TQ in patients with a history of a psychiatric disorder and this reviewer agrees with the applicant's proposal to include a warning to that effect in the TQ package insert. PQ would be an option for these patients because it does not include psychiatric adverse reactions in its USPI and it has a known safety profile after decades of clinical use.

9.1.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not Applicable.

Pediatrics and Assessment of Effects on Growth

Not Applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not Applicable.

9.1.9.Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not Applicable.

Expectations on Safety in the Postmarket Setting

Not Applicable. See section 9.2.

9.2. Integrated Assessment of Safety

Healthy Volunteer Studies of TQ

Three healthy volunteer studies evaluated TQ single dose alone compared to PQ or placebo. Gastrointestinal adverse reactions were relatively uncommon. TQ was administered with food and was generally well tolerated. Nausea was the most common symptom and occurred in less than 10% of subjects.

The most common neurologic adverse reaction was dizziness. Dizziness appeared to be related to TQ at all doses. All cases of dizziness were mild, of short duration, and resolved spontaneously. Dizziness is also associated with the other 8-aminoquinoline, PQ.

One subject without a psychiatric medical history developed depressed mood after treatment with TQ 600 mg which resolved spontaneously after three days.

Hypersensitivity reactions manifested by symptoms such as angioedema and urticaria occurred in two healthy subjects approximately two weeks post treatment in TQT study, TAF114582. Hypersensitivity reactions were not reported with TQ in the other single-dose healthy volunteer studies or clinical trials in the development program.

Asymptomatic decreases in Hgb of 1g/L to <3g/dL were associated with TQ use; no patient required blood transfusion.

Asymptomatic increases in methemoglobin (MetHb%) were observed in some patients. In the small number of G6PD-deficient subjects, declines in Hgb and increases in MetHb% were higher than G6PD-normal subjects as would be expected for an 8-aminoquinoline drug.

Transient mild elevations in hepatic transaminases were reported.

No significant QTc prolongation effect of TQ was detected in the TQT study, TAF114582, see section 9.1.4.

There were no reports of keratopathy or retinal changes in the ophthalmologic safety study, 201807.

TQ appears to have a similar hematologic safety profile to PQ in healthy individuals. The decreases in Hgb levels observed in G6PD-normal subjects in this study correlate with the findings in the placebo (CQ)-controlled trials in G6PD-normal patients with *P. vivax* malaria which reported a higher frequency of mild, asymptomatic, reversible declines in Hgb in the TQ+CQ arm as compared to CQ alone.

The numbers of subjects in the healthy volunteer studies are relatively small; however, it appears that TQ has a safety profile similar to the PQ, except for two case reports of hypersensitivity and one case of depressed mood. TQ was reasonably safe and well tolerated in healthy individuals.

Clinical Trials of TQ plus CQ in *P. vivax* malaria

The safety of TQ+CQ was compared to CQ and/or PQ+CQ in the phase 2b dose-escalation trial, TAF112582 part 1 and in two phase 3 clinical trials, TAF112582 part 2 and TAF116564. These trials evaluated the efficacy and safety of the proposed regimen of TQ 300mg single-dose with CQ x 3 days for treatment of *P. vivax* malaria. There were no deaths in the TQ development program and no patients were withdrawn from the trials for an adverse event.

Gastrointestinal: Gastrointestinal adverse events were the most common events observed in the three clinical trials. TQ was administered with food. As in the healthy volunteer studies, nausea was the most common adverse event associated with TQ +CQ in patients with *P. vivax* malaria.

Cardiac: In TAF112582 part 1 &2, differences in QTc between treatment groups were not considered to be clinically significant. There were three subjects in the CQ group who met protocol-specified stopping rules for study medication discontinuation due to QTc prolongation. No additional effect on the QT interval was observed when TQ was added to CQ.

Ophthalmologic: In TAF112582 part 2, one case of unilateral vortex keratopathy, not associated with changes in vision, was detected at Day 90 in the TQ 300mg + CQ group. There were no reports of vortex keratopathy in the phase 2B study in patients who received TQ 50 mg to 600mg but it is not clear if all appropriate ophthalmic testing was performed. Reversible vortex keratopathy without visual abnormalities has been reported in malaria prophylaxis trials of TQ with up to 6 months of dosing.

Neuropsychiatric: Neuropsychiatric adverse events were infrequent in the three phase 2b/3 trials. Insomnia was the most common neurologic adverse reaction occurring in approximately 3% of subjects in the TQ+CQ, PQ+CQ, and CQ treatment groups. In the placebo (CQ)-controlled trials, more patients reported dizziness in the TQ 300mg+CQ group as compared to CQ group, i.e., 25(7.9%) vs. 6 (3.2%).

Anxiety was reported in 2(< 1%) patients in the TQ+CQ group which developed within the first five days of treatment in TAF112582 part 2; there were no cases of anxiety in the PQ+CQ and CQ groups. One of the patients received diazepam for anxiety and insomnia and symptoms

resolved within five days. The close temporal relationship suggests an association between anxiety and TQ. Overall, anxiety was reported with TQ+CQ and PQ+CQ, i.e., in five patients, 2 (0.4%) TQ+CQ versus 3 (1.1%) PQ+CQ treatment groups in the phase 2b/3 clinical trials. The patients fully recovered. Psychosis was reported in two subjects who received TQ single dose 350mg or 500mg during the clinical development program (one patient had history of two prior psychotic episodes and one had been recently diagnosed with schizophrenia).

Neuropsychiatric adverse events are associated with the 4-quinoline-methanol, MQ, and much less so with the 8-aminoquinoline, PQ. An association between TQ 300mg and neuropsychiatric adverse reactions, i.e., dizziness, insomnia, and anxiety cannot be ruled out. The risk of developing a serious psychiatric adverse event is probably low with a single dose of TQ 300mg; however, it would be appropriate to avoid TQ in patients with a history of psychiatric disorder based on the cases described. See section 9.1.5.

Immunologic: No cases of hypersensitivity were reported in the phase 2b/3 clinical trials. Pruritus was reported across all treatment groups and appeared to be associated with CQ; pruritus is a known side-effect of CQ. Pruritus was not associated with skin rash or other allergic symptoms.

Laboratory Abnormalities

Hemoglobin: TQ+CQ was associated with the development of hemolysis in patients with G6PD deficiency. Decreases in Hgb levels from baseline were also observed in TQ 300mg + CQ regimen in G6PD-normal (defined as a G6PD activity > 70%) subjects in the three clinical trials. In the phase 3 trial, TAF112582 part 2, Hgb decreases of >3.0g/dL (a protocol defined SAE for hemolysis) occurred across the treatment arms, TQ 300mg+CQ (5%) vs. PQ+CQ (2%) vs. CQ (2%). Over 80% of patients experienced decreases in Hgb from 0 to ≤ 2 g/dL across the three treatment arms which were not considered clinically significant. Patients were asymptomatic and Hgb recovered to baseline levels without medical intervention such as blood transfusion. The pattern of Hgb decline associated with mild increases in reticulocyte counts and subsequent improvement of Hgb to baseline levels or higher was consistent with recovery from *P. vivax* malaria. It is difficult to distinguish drug-induced hemolysis from underlying hemolysis due *P. vivax* malaria. The frequency of Hgb decreases was higher in the TQ 300mg+CQ treated group as compared to PQ+CQ or CQ alone; therefore, TQ 300mg +CQ may have contributed to the declines in Hgb. Rehydration may have been another factor that contributed to the observed declines in Hgb due to increased intravascular volume. Elevation in urea levels, an indicator of dehydration, were present in ~ 25% to 30% of patients at baseline in all treatment groups. Monitoring of hemoglobin levels would be particularly important in patients with *P. vivax* malaria who are anemic at presentation.

G6PD deficiency: Patients with phenotypic G6PD deficiency were excluded from the placebo-controlled trials based on a quantitative enzymatic assay. The enzymatic assay failed to exclude three females with G6PD genetic mutations from the phase 2b trial; however, none of these three patients experienced decreases in hemoglobin > 2.5g/dL, a predefined SAE in the study protocol.

Other hematological parameters: The changes from baseline in other hematological parameters such as white blood count and platelet counts were generally not clinically significant. Eosinophilia was observed across all treatment groups and was associated with documented helminth infections (< 1 to 2%) of subjects in the treatment arms, suggesting that this may have been the cause of the eosinophilia rather than the effect of study drugs.

Methemoglobin: Methemoglobinemia is associated with PQ. Increases in MetHb% were observed in the phase 2b/ 3 clinical trials; however, there were no serious adverse events associated with increases in methemoglobin levels. The largest mean increase in MetHb% was observed in the PQ+CQ treatment group. Maximum MetHb% levels were approximately 13% (< 3% normal) and was considered clinically acceptable from a safety perspective because patients had no clinical signs of methemoglobinemia except for a complaint of fatigue.

Hepatic: Elevated transaminases and bilirubin at baseline associated with *P. vivax* malaria were observed in all treatment groups. ALT levels returned to normal range post treatment. Elevated ALT levels post baseline were observed in the TQ+CQ group, for example, two patients in the TQ 300mg +CQ group developed elevated transaminases (< 5x ULN) on treatment which resolved spontaneously. One patient had an SAE of elevated ALT > 10x ULN which was probably related to ingestion of herbal medicines but an effect of TQ+CQ cannot be ruled out. ALT/AST levels returned to the normal range post treatment.

In the phase 2b study dose ranging trial, there were no major differences between the treatment groups, TQ 50 mg to 600mg, in maximum changes from baseline in hepatic transaminases.

Significant posttreatment elevations in ALT were associated with concurrent hepatitis B, hepatitis E, or relapse/recurrence of *P. vivax* malaria. Elevations in total bilirubin (>2x ULN) at baseline in patients with malaria and at early time points during treatment were observed in all treatment groups and bilirubin levels returned to within normal limits for most subjects in the first week post treatment.

Creatinine: Elevations in serum creatinine associated with study drugs was observed in the TQ+CQ treatment group. Elevations in creatinine from baseline were mild and transient and were possibly related to effects of TQ on renal transporters.

CPK: Elevations in CPK levels were observed in all treatment groups and were related to strenuous exercise and muscle injury in many patients but remained unexplained in some subjects. Elevation in CPK was not associated with renal injury. There were no cases of rhabdomyolysis.

Conclusions

TQ 300mg single-dose was generally well-tolerated during the clinical development program. The safety profile of TQ was consistent with the known safety profile of PQ, an 8-aminoquinoline drug. There was no evidence that TQ exacerbates the adverse effects of CQ in the phase 2b/3 clinical trials.

TQ 300mg single dose administered with a 3-day course of CQ was found to be reasonably safe for the treatment of *P. vivax* malaria in the subjects with G6PD enzyme activity > 70%. Patients must have G6PD testing done before starting TQ to avoid the risk of hemolytic anemia. Safety data is negligible for patients with G6PD enzyme activity in the 40 to 60% range and TQ (and PQ) must not be prescribed to patients with G6PD enzymatic activity < 70% of normal. Reliable assays should be used to make the diagnosis of G6PD deficiency; as seen in one phase 3 trial, three patients with G6PD deficiency were enrolled based on a false negative screening test for G6PD deficiency.

Decreases in Hgb levels of > 3g/dL (a protocol defined SAE) were observed in G6PD normal (i.e., > 70% enzyme activity) patients at a higher incidence in those who received TQ 300mg + CQ than in patients treated with CQ. The decreases in Hgb levels were not in the anemic range in most patients. Patients were asymptomatic and Hgb levels recovered without medical interventions such as blood transfusion. Overall, the reported reversible declines in Hgb levels observed in these patients were acceptable from a safety perspective. Monitoring of hematologic parameters such as hemoglobin in patients treated with TQ+CQ is warranted and it is particularly important in patients with *P. vivax* malaria who present with anemia.

TQ 300mg single-dose treatment has an advantage over the 7- or 14-day course of PQ regarding compliance with treatment and greater compliance should lead to decreases in relapses of *P. vivax* malaria and improved clinical outcomes. TQ may also help to reduce transmission of *P. vivax* in endemic areas.

A disadvantage of TQ's long elimination half-life is that drug-induced adverse events cannot be curtailed by stopping drug administration as is the case with PQ which has a shorter half-life, $T_{1/2}$ ~ 6 hours. Hypersensitivity reactions were seen at 2 weeks following TQ single-dose in two subjects in a healthy volunteer study. It is important that clinicians to be aware that the 15-day half-life of TQ and long half-life of CQ may impact the onset and duration of adverse reactions.

A limitation of the 8-aminoquinolines is that for safety reasons, neither PQ nor TQ can be used in pregnant or lactating women because of the risk of acute hemolytic anemia in a G6PD-deficient fetus or breast-fed infant. TQ is contraindicated in pregnancy because the G6PD status of the fetus is not known even if the mother is G6PD normal. TQ has not been studied in pregnant women or in lactating women. No animal or human studies have been conducted to determine if TQ is excreted in breast milk. A recent publication has shown that the concentration of PQ in breastmilk is low and suggests that PQ could be safe even for G6PD deficient infants beyond the neonatal period.[27]

10 Advisory Committee Meeting and Other External Consultations

[27] Gilder ME, Hanpithakphong W, Hoglund RM, *et al*. PQ pharmacokinetics in lactating women and breast- fed infant exposures. Clin Infect Dis 2018, Mar 24. doi: 10.1093/cid/ciy235. [Epub ahead of print]

An Advisory Committee meeting was held on July 12th, 2018 to discuss NDA 210795. The following two questions were posed to the committee.

1. Has the applicant provided substantial evidence of the effectiveness of TQ for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients 16 years of age and older?
   If yes, please provide any recommendations concerning labeling.
   If no, what additional studies/analyses are needed?

Committee Vote
Yes: 13, No: 0

2. Has the applicant provided adequate evidence of the safety of TQ for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients 16 years of age and older?
   If yes, please provide any recommendations concerning labeling.
   If no, what additional studies/analyses are needed?

Committee Vote
Yes: 12, No: 1.

11 Pediatrics

TQ for the radical cure of *P. vivax* malaria has orphan drug designation. There were no pediatrics studies in the NDA.

12 Labeling Recommendations

12.1. Prescribing Information

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
Contraindication	G6PD deficiency	G6PD deficiency and unknown G6PD status
Warnings and Precautions	Contraindication in pregnancy or breast-feeding	G6PD deficiency in pregnancy or breast-feeding is in Warnings and Precautions

12.2. Patient Labeling

The Applicant has proposed a patient Information labeling to inform patients of key information for safe and effective use of KRINTAFEL. Patient Labeling review team has provided edits for clarity and consistency with KRINTAFEL package insert. The Applicant has accepted the proposed changes.

13 Risk Evaluation and Mitigation Strategies (REMS)

13.1. Safety Issue(s) that Warrant Consideration of a REMS

A REMS is not recommended.

14 Postmarketing Requirements and Commitments

During the July 12, 2018, Advisory Committee, one of the speakers at the open public hearing raised a question regarding the potential neurotoxic effects of TQ and need for additional nonclinical studies. This was based partly on publications describing the neurotoxicity of other 8-aminoquinolines in monkeys. The publications describe lesions in various areas of the brain, predominantly in the vestibular nuclei and in the nuclei of the proprioceptive and visual-reflex pathways. Schmidt et al. (1951) reported that the lesions associated with the use of plasmocid were accompanied by neurobehavioral changes, whereas lesions seen with the administration of pentaquine, isopentaquine, and PQ did not result in neurobehavioral symptoms.[28]

We have reviewed the histopathology reports including brain tissue from repeat dose studies in several species and have found no adverse neurohistological changes. The rat studies submitted in the NDA, conducted specifically to evaluate the neurotoxic potential of TQ, did not demonstrate any behavioral or histological evidence of neurotoxicity. We have carefully considered the question of whether studies in NHPs with TQ are needed at this time as part of the evaluation for histopathologic effects, behavioral changes, and neuropsychiatric effects. Studies in more than one species (rats and dogs) administered single and repeat doses of oral TQ at exposures similar or greater than the 300-mg single dose in humans, showed no specific findings of neurotoxicity. In the published literature, animal studies conducted with another 8-aminoquinoline, plasmocid, in rats and dogs showed evidence of adverse neurologic symptoms and histological changes suggesting these species demonstrated some sensitivity to the neurotoxic potential of 8-aminoquinolines (Richter 1949; Schmidt 1949).[29, 30] The NHP findings with PQ were observed in monkeys at lethal or near lethal doses, at approximately 15 times greater than the tested clinical dose (by body surface area comparison). Considering the data from toxicology studies in rats and dogs with TQ, the findings from plasmocid toxicology studies in rats and dogs, the available clinical data and the plan for pharmacovigilance to specifically monitor for neuropsychiatric adverse effects, our assessment is that an NHP study to evaluate neurologic, behavioral, and neuropsychiatric effects with TQ is not warranted. We will continue to monitor for neurologic and neuropsychiatric effects during the postmarketing period and

[28] Schmidt et al. (1951). Neurotoxicity of the 8-aminoquinolines. J. Neuropathol. Exp. Neurol. 10(3): 231-255
[29] Richter R (1949). The effect of certain quinoline compounds upon the nervous system of monkeys. J Neuropathol Exp Neurol. 1949 Apr;8(2):155-70.
[30] Schmidt and Schmidt (1949). Neurotoxicity of the 8-aminoquinolines.

from the data assembled from the postmarketing requirement that includes a specific focus on neuropsychiatric adverse effects.

After the July 12, 2018, Antimicrobial Drugs Advisory Committee meeting, the agency had asked the Applicant to comment on the need for additional nonclinical or clinical studies to evaluate the neurotoxic potential of TQ and the types of studies that might be best suited for this purpose.
The Applicant responded that they have conducted a thorough nonclinical evaluation of TQ, including two studies in rats specifically designed to look at neurobehavioral effects and found no evidence of TQ neurotoxicity and therefore believes that no additional nonclinical studies are necessary.

In addition, they noted that several decades of clinical experience with PQ have not revealed an association between PQ and psychiatric or neurologic adverse reactions. The applicant also indicated that this clinical observation confirms the assumption by Schmidt at al. (1951) that "the results of the present study indicate little likelihood that significant neuronal injury would result from clinical use of either pentaquine, isopentaquine, primaquine or pamaquine in doses such as are employed in malaria therapy."

The Applicant indicated that TQ 300 mg single dose has not been associated with any severe, serious, persistent, or otherwise concerning neurologic or psychiatric adverse effects. In the premarketing safety database including controlled clinical trials, psychiatric and neurological adverse reactions occurred infrequently and at similar rates between PQ-treated patients and TQ-treated patients at the to-be-marketed dose. . There were cases of psychiatric adverse reactions that occurred at doses higher than the to-be-marketed dose in healthy volunteer studies, but 3 of the 4 cases occurred in patients with pre-existing psychiatric conditions. The fourth case was mild depression that resolved in 3 days after TQ treatment.

Overall, our assessment is that the clinical data are more informative in evaluating the potential for TQ to cause adverse psychiatric and neurological than additional animal studies. It would be very difficult to study behavioral and psychiatric toxicities in animals. Moreover, psychiatric effects are likely unrelated to the central nervous system lesions observed in some of the animal studies with 8-aminoquinolones. As to relevance of the structural central nervous system lesions observed in animals to humans, extensive clinical experience with PQ provides no convincing evidence that 8-aminoquinolones when administered at therapeutic doses result in psychiatric or neurologic adverse effects. Furthermore, even if additional animal studies were conducted to determine if TQ induces neurobehavioral or structural changes in animals, its effects in humans would not be addressed.

The approval of NDA 210795 will include a postmarketing requirement e to conduct an active pharmacovigilance surveillance study to specifically solicit for neuropsychiatric adverse reactions, as well as hypersensitivity and hematological adverse reactions. Although there are limitations to pharmacovigilance studies that include the lack of a control group, it is appropriate in this case where the TQ pre-approval safety database contains a PQ control

group. Based on the data generated from this study and routine pharmacovigilance, labeling revisions will be made as needed.

The following postmarketing requirement was agreed with the Applicant:

3436-1: Conduct an active pharmacovigilance study to evaluate safety, including hypersensitivity, neuropsychiatric and hematologic adverse reactions, in patients taking KRINTAFEL (Tafenoquine) for the radical cure of *P. vivax* malaria.

Draft Protocol Submission:	10/2018
Final Protocol Submission:	04/2019
Interim Report Submission:	09/2020
	09/2021
	09/2022
	09/2023
	09/2024
Study Completion:	12/2024
Final Report Submission:	09/2025

15 Appendices

15.1. References

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15.2. Financial Disclosure

[Insert text here.]

Covered Clinical Study (Name and/or Number): TAF112582, TAF 116564, and 058

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: **94**		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): **None**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **None**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) **0**		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

not applicable

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

15.4.1. Summary of Bioanalytical Method Validation and Performance

Table 1 describes the summary of the bioanalytical methods used for quantification of TQ in human plasma and blood (See Table 2 for details). The analytical method validation and performance are acceptable.

Table 1. Summary of Bioanalytical Methods for Quantification of TQ

Analytical Method	Matrix	Validated Range	Study Number
HPLC with fluorescence detection	Plasma	0.815 to 408 ng/mL	50
	Blood	1.91 to 383 ng/mL	
HPLC-MS/MS	Plasma	2 to 500 ng/mL	14, 15
HPLC-MS/MS	Plasma	5 to 500 ng/mL	22, 40
HPLC-MS/MS	Plasma	1-3000 ng/mL	TAF106491, TAF110027
HPLC-MS/MS	Plasma	2-3000 ng/mL	TAF112582 (Part 1 and Part 2) TAF114582 TAF116554, 200951 201807
HPLC-MS/MS	Plasma	0.5 to 500 ng/mL	201780

Table 2. Validation Reports for Quantification of TQ in Plasma and Blood (Adapted from Applicant's Bioanalytical Methods Summary)

Validation Report	Study Number	Method Description and Performance	
RSD-1016TL	50	Tafenoquine was extracted from 0.2 mL human plasma and blood by protein precipitation using methyl t-buytl ether containing internal standard (b) (4) Extracts were analysed by HPLC with a chiral column with fluorescence detection	
		Analyte	Tafenoquine
		Calibration Model	Not stated
		Validated Range	Plasma: 0.815 to 408 ng/mL Blood: 1.91 to 383 ng/mL
		QC Samples	Plasma: 1.63, 20.4, 81.5, 163 ng/mL Blood: 3.82, 19.1, 76.5, 143 ng/mL
		Within Run Precision (%CV)	Plasma: ≤ 9.07% Blood: ≤ 9.15%
		Between Run Precision	Plasma: ≤ 8.70% Blood: ≤ 7.75%
		Accuracy (bias%)	Plasma: -4.68% ≤ bias ≤ 31.7% Blood: -22.7% ≤ bias ≤ -5.86%
		Stability of stock solution	Not determined
		Freeze-Thaw Stability	Not determined
		Processed Sample Stability	Not determined
		Stability in Blood	Not determined
		Stability in Plasma	Plasma: At least 143 days at -20°C Blood: Up to 62 days at -20°C
		Matrix Dilution	Not determined
		Recovery	Plasma: 76.3% to 89.5% Blood: 89.1% to 106%
RSD-1013VC/1	14, 15	Tafenoquine was extracted from 50 µL of human plasma by protein precipitation using methanol spiked with (b) (4) (b) (4) as an internal standard. Extracts were analysed by HPLC-MS/MS (positive ion) using a Turbolonspray interface.	
		Analyte	Tafenoquine
		Calibration Model	Linear weighted $1/x^2$
		Validated Range	2 to 500 ng/mL
		QC Samples	2, 8, 200 and 500 ng/mL
		Within Run Precision (%CV)	≤ 6.46%
		Between Run Precision	≤ 7.24%
		Accuracy (%bias)	-3.69 % ≤ Bias ≤ 3.45%
		Stability of stock solution	Not determined
		Freeze-Thaw Stability	At least 3 cycles from -70°C to ambient temperature
		Processed Sample Stability	Not determined
		Stability in Plasma	Not determined
		Stability in Blood	
		Matrix Dilution	Not determined
RSD-101CSX/1 W2204-00374	22, 40	Tafenoquine was extracted from 50 µL of human plasma by protein precipitation using methanol spiked with ([2H4 15N]-tafenoquine,as an internal standard. Extracts were analysed by HPLC-MS/MS (positive ion) using a Turbolonspray interface.	
		Analyte	Tafenoquine
		Calibration Model	Linear weighted $1/x^2$
		Validated Range	5 to 500 ng/mL
		QC Samples	5, 20, 200,500 ng/mL
		Within Run Precision (%CV)	≤ 5.84%
		Between Run Precision	≤ 7.32 %
		Accuracy (%bias)	1.54% ≤ Bias ≤ 4.38%
		Stability of stock solution	Not determined
		Freeze-Thaw Stability	Not performed in this validation – See RSD-1013VC
		Processed Sample Stability	Not determined
		Stability in Plasma	At least 3 months at -20°C
		Stability in Blood	Not determined
		Matrix Dilution	Not determined

Validation Report	Study Number	Method Description and Performance	
FD2007/00202	TAF106491, TAF110027	Tafenoquine, chloroquine and desethyl chloroquine was extracted from 50 µL human plasma by protein precipitation using acetonitrile containing isotopically labelled internal standards ([2H4 15N]-tafenoquine and (b) (4) Extracts were analysed by HPLC-MS/MS using a Turbolonspray interface with multiple reaction monitoring.	
		Analyte	Tafenoquine, chloroquine, desethyl chloroquine
		Calibration Model	Linear weighted 1/x²
		Validated Range	1-3000 ng/mL
		QC Samples	1, 4, 16, 500, 2400 and 3000 ng/mL
		Within Run Precision (%CV)	Tafenoquine: ≤ 6.4% Chloroquine: ≤ 11.0% Desethyl chloroquine: ≤ 11.7%
		Between Run Precision	Tafenoquine: ≤ 1.2% Chloroquine: ≤ 1.2% Desethyl chloroquine: ≤ 10.4
		Accuracy (%bias)	Tafenoquine: -1.9% ≤ Bias 3.8% Chloroquine: -4.5% ≤ Bias 5.1% Desethyl chloroquine: -9.5% ≤ Bias 12.2%
		Stability of stock solution	Tafenoquine (DMF): At least 40 days at 4˚C (b) (4) Chloroquine (water): At least 40 days at 4˚C Desethyl chloroquine (water): At least 10 days at 4˚C (b) (4)
		Freeze-Thaw Stability	All analytes: At least 3 cycles from -80°C
		Processed Sample Stability	Tafenoquine: At least 48 hours at ambient temperature (b) (4) Chloroquine (water): At least 120 hours at ambient temperature (b) (4) Desethyl chloroquine (water): At least 120 hours at ambient temperature (b) (4) (b) (4)
		Stability in Plasma	All analytes: At least 24 hours at ambient temperature
		Stability in Blood	Not determined
2011N118212 2017N325927 2017N321883	TAF112582 (Part 1 and Part 2) TAF114582 TAF116554, 200951 201807	Tafenoquine, chloroquine and desethyl chloroquine were extracted from 25 µL human plasma by protein precipitation using methanol containing isotopically labelled internal standards ([2H4 15N]-tafenoquine (b) (4) (b) (4) Extracts were analysed by HPLC-MS/MS using a Turbolonspray interface with multiple reaction monitoring.	
		Analyte	Tafenoquine, CCI5360, GW346905
		Calibration Model	Linear weighted 1/x²
		Validated Range	2-3000 ng/mL
		QC Samples	2400, 500, 16 and 6 ng/mL
		Within Run Precision (%CV)	Tafenoquine: ≤ 8.2% Chloroquine: ≤ 10.1% Desethyl chloroquine: ≤ 11.6%
		Between Run Precision	Tafenoquine ≤ 4.1% Chloroquine: ≤ 2.1% GW346905: ≤ 3.7
		Accuracy (%bias)	Tafenoquine: -6.9% ≤ Bias 7.4% Chloroquine: -6.8% ≤ Bias 5.1% Desethyl chloroquine: -9.7% ≤ Bias 8.3%
		Stability of stock solution	Tafenoquine (DMF): At least 33 days at 4˚C At least 24 hours at room temperature Chloroquine (water): At least 33 days at 4˚C At least 24 hours at room temperature Desethyl chloroquine (water): At least 33 days at 4°C At least 24 hours at room temperature
		Freeze-Thaw Stability	At least 3 cycles from -20°C to ambient temperature
2016N271669	201780	Tafenoquine, [15N13C4]-tafenoquine, chloroquine and desethyl chloroquine were extracted from 7 µL human plasma by protein precipitation using methanol plus 0.1% formic acid containing isotopically labelled internal standards ([2H413C515N]-tafenoquine (b) (4) Extracts were analysed by LC-MS/MS using a ZSpray interface with multiple reaction monitoring. Stability in microcapillaries were also investigated	
		Analyte	Tafenoquine, tafenoquine -M+5, chloroquine and desethyl chloroquine.
		Calibration Model	Linear weighted 1/x²
		Validated Range	0.5 to 500 ng/mL for all analytes
		QC Samples	0.5, 1.5, 50, 375, 500 ng/mL
		Within Run Precision (%CV)	Tafenqouine: ≤10.4% [15N13C4]-tafenoquine: ≤10.8% Chloroquine: ≤12.4% Desethyl chloroquine: ≤13.9%
		Between Run Precision	Tafenoquine: ≤4.3% [15N13C4]-tafenoquine: ≤10.4% Chloroquine: ≤15.0% Desethyl chloroquine: ≤10.3%

Validation Report	Study Number	Method Description and Performance	
		Accuracy (%)	Tafenoquine: 90.7% ≤ Accuracy ≤101.1% [15N13C4]-tafenoquine:88.5% ≤ Accuracy ≤109.5% Chloroquine:88.6% ≤ Accuracy ≤116.0% (LLQ) Desethyl chloroquine:86.3% ≤ Accuracy ≤116.9% (LLQ)
		Stock Solution Stability of [15N13C4]-tafenoquine in DMF (1 mg/mL), chloroquine and desethyl chloroquine in water (1 mg/mL)	At least 35 days at 4°C At least 24 hours at room temperature
		Working Solution Stability in Water/Acetonitrile (50/50, v/v) (20 µg/mL)	Chloroquine: At least 4 hours at room temperature Tafenoquine; [15N13C4]-tafenoquine; desethyl chloroquine: At least 24 hours at room temperature All analytes: At least 22 days at 4°C
		Freeze-Thaw Stability	At least 3 cycles from -20°C to ambient temperature and at least 3 cycles from -80°C to ambient temperature
		Processed Sample Stability	At least 75 hours at ambient temperature
		Stability in human plasma tafenoquine * in presence of all analytes ** combined (tafenoquine with chloroquine or [15N 13C4]-tafenoquine with desethyl chloroquine).	At least 19 hours at room temperature At least 143 days at -20°C * At least 141 days at -80°C * At least 45 days at -20°C ** At least 45 days at -80°C **
		Stability in human plasma [15N13C4]-tafenoquine * in presence of all analytes ** combined (tafenoquine with chloroquine or [15N 13C4]-tafenoquine with desethyl chloroquine).	At least 24 hours at room temperature At least 143 days at -20°C * At least 141 days at -80°C * At least 43 days at -20°C ** At least 43 days at -80°C **
		Stability in human plasma of chloroquine * in presence of all analytes ** combined (tafenoquine with chloroquine or [15N 13C4]-tafenoquine with desethyl chloroquine).	At least 24 hours at room temperature At least 143 days at -20°C * At least 141 days at -80°C * At least 45 days at -20°C ** At least 45 days at -80°C **
		Stability in human plasma of desethyl chloroquine	At least 24 hours at room temperature

Validation Report	Study Number	Method Description and Performance	
		Stability in human whole blood	At least 2 hours at 37°C
		Stability in human whole blood in the capillary	Tafenoquine; [15N13C4]-tafenoquin: At least 2 hours at room temperature Tafenoquine; [15N13C4]-tafenoquine; desethyl chloroquine: At least 2 hours in ice Chloroquine: At least 1 hour in ice
		Stability in human centrifuged blood in the capillary	Tafenoquine; [15N13C4]-tafenoquine; desethyl chloroquine: At least 2 hours at room temperature Tafenoquine; [15N13C4]-tafenoquine; desethyl chloroquine: At least 2 hours in ice Chloroquine: At least 1 hour in ice
		Homogeneity in human plasma in the capillary	At least 2 hours at 4°C
		Matrix Dilution	20-fold in human plasma
		Carry-Over	Tafenoquine: <51.3% [15N 13C4]-tafenoquine: <58.4% Chloroquine: <28.7% Desethyl chloroquine: <43.6% All internal standards: <5% Carry Over IS

15.4.2.Population PK Analysis

STUDY NO.: 2017N331946

Population Meta-Pharmacokinetic Analysis Report of TQ in Patients with *Plasmodium Vivax* Malaria.

OBJECTIVES

The objectives of this study are listed below:

- To characterize the POP PK of TQ (TQ) following oral administration to subjects with *P. vivax* malaria
- To characterize any potential impact of the two formulations on systemic TQ exposure.
- To characterize any potential impact of selected subject covariates on systemic TQ exposure.

The endpoints of this study are:

- Population estimates of PK parameters (e.g. CL/F, V2/F), associated inter-subject variability and residual error.
- Estimates of relative bioavailability of formulations.
- Other covariates impacting the PopPK parameters and consequently the systemic exposure of TQ.

DATA SOURCE

Data from 5 studies (TAF112582 part 1 and TAF112582 part 2; Study 200951; Study 201780 and TAF114582) are included for the POP PK analyses. Data from the TAF116564 study were used for the external model validation.

All studies were randomized, parallel design studies. Except for TAF114582 study, TQ was administered as a single dose in all studies. In TAF114582 study, TQ was administered as single dose for the 300 and 600 mg cohorts. For the 1200 mg supratherapeutic dose, TQ was administered as 400 mg once daily for three days. Table 1 provides a summary of studies used in population PK analyses.

TAF112582: This study was a multi-center, double-blind, double-dummy, parallel group, randomized, active control study to evaluate the efficacy, safety and tolerability of TQ in subjects with *P. vivax* malaria. The study was conducted in two parts (Part 1 Phase 2 dose ranging study and Part 2 Phase 3 study). In Part 1 study, PK data from a total of 223 patients with *P. vivax* malaria were included. Patients who received TQ were divided in 4 cohorts: 50, 100, 300, or 600 mg single dose (Day 1 or Day 2) with co-administration of CQ (CQ) (600 mg once daily on Days 1 and 2, 300 mg once daily on Day 3).. In Part 2 study, PK data from 259

patients with *P. vivax* malaria who received TQ 300 mg single dose (Day 1 or Day 2) with co-administration of CQ (600 mg once daily on Days 1 and 2, 300 mg once daily on Day 3) were included. Five samples per subject were collected in Part 1 and Part 2 studies for PK assessment: 2 sample windows (4-8h and 24-48h post TQ dosing), and on days 8, 29 and 60.

Study 200951: This study was a single-center, 5-cohort, randomized open-label, parallel-group study to evaluate the pharmacokinetics of a single dose of TQ 300mg when co-administered with the artemisinin-based combination therapies (ACT), artemether + lumefantrine (AL) and dihydroartemisinin + piperaquine tetraphosphate (DHA+PQP) in healthy volunteers. PK data from 24 subjects that received TQ 300 mg alone treatment were included in the PopPK analysis. Eighteen blood samples per subject were collected for PK assessment at Day 1 through 72 hours and at Days 7, 14, 21, and 28 post dose.

Study 201780: This study was a single-center, 2-arm, randomized open-label, parallel-group study in healthy volunteers to determine the effects of dissolution profile on the pharmacokinetics (via both venous and peripheral microsamples) of single oral 300 mg doses of TQ tablets + 30 mg TQ stable isotope labelled (SIL) solution. PK data from all 14 subjects randomized to receive the intermediate aged or control TQ 300 mg single dose were included in this study. Seventeen PK samples per subject were collected from Day 1 through 72 hours post first dose and at Days 7, 14, 21, 28 and 56 post first dose.

TAF114582: This study was a randomized, placebo-controlled study to evaluate the effect of TQ on the electrocardiogram with focus on cardiac repolarization (QTc duration) in healthy subjects. PK data from a total of 155 subjects who received TQ 300 mg single dose, 600 mg single dose or 400 mg once daily for 3 days were used for the analysis. Sixteen PK samples per subject were collected from Day 1 through 72 hours post the last dose.

TAF116564: This study was a prospective, double-blind, double-dummy, multicenter, comparative study to assess the incidence of hemolysis, safety, and efficacy of TQ versus PQ in the treatment of subjects with *P. vivax* malaria. PK data from a total of 166 subjects who received 300 mg TQ single dose (Days 1 or 2) in combination of CQ (600 mg once daily on Days 1 and 2, 300 mg once daily on Day 3) were included in this study. Sparse samples were collected on Days 2, 3, 8, 15, 29 and 60 of the study for pharmacokinetic analyses.

A total of 6375 records (788 are dosing records, 90 pre-dose sampling records, 5497 TQ systemic concentration observations) from 675 subjects receiving TQ are included in the analyses dataset. This dataset includes data from 5 studies (TAF112582 part 1, TAF112582 part 2, Study 200951, Study 201780 and TAF114582) and excludes data from the TAF116564 study. A summary of subject demographics and key clinical covariates is provided in **Table 2**. The summary of demographics for the TAF116564 (patient study) data is provided in **Table 3**. These demographics are comparable to the TAF112582 part 2 (patient study) demographics and thus was utilized to validate the PopPK model generated with the dataset containing the TAF112582 data.

Table 1. Summary of data used for population PK analysis and external model validation

Study	No. of Subjects*	Dose (mg)	Formulation	Status
200951	24	300	Tablet	Healthy
201780	14	300	Tablet	Healthy
TAF114582	155	300, 600, 1200	Capsule	Healthy
TAF112582 Part 1	223	50, 100, 300, 600	Capsule	Patients
TAF112582 Part 2	259	300	Tablet	Patients
TAF116564	166	300	Tablet	Patients

* Subject numbers listed here indicate subjects from the tafenoquine only arms that were included in the current analyses.

Source: Applicant's population PK report (Study 2017n331946 Report), Page 11, Table 1

Table 2. Summary of key demographics and covariates of subjects included in the analyses dataset from 5 studies

Age in years, median (range)	35.0 (15.0-79.0)
Gender, Number (% of total subjects in dataset)	
Female	171 (25.3%)
Male	504 (74.7%)
Weight in kg, median (range)	69.3 (37.2-138.3)
Body Mass Index, in kg/m2, median (range)	24.3 (15.5-47.0)
Health Status, Number (% of total subjects in dataset)	
Healthy volunteers	193 (28.6%)
Patients	482 (71.4%)
Formulation Status, Number (% of total subjects in dataset)	
Tablet formulation	297 (44.0%)
Capsule formulation	378 (56.0%)
Race, Number (% of total subjects in dataset)	
Caucasian Heritage	95 (14.1%)
African American Heritage	123 (18.2%)
Asian Heritage	160 (23.7%)
American Indian/Alaskan native Heritage	193 (28.6%)
Other	1 (0.1%)
Multiple	103 (15.3%)

This table includes data from the 5 studies (DETECTIVE part 1, Detective part 2, DDI, SIL and TQT study)

Source: Applicant's population PK report (Study 2017n331946 Report), Page 16, Table 2

Table 3 Summary of key demographics and covariates of subjects included in TAF116564 Study

Age in years, median (range)	36.0 (16.0-75.0)
Gender, Number (% of total subjects in dataset) Female Male	 52 (31.3%) 114 (68.7%)
Weight in kg, median (range)	64.8 (38.0-122.8)
Body Mass Index, in kg/m2, median (range)	24.9 (16.7-48.9)
Race, Number (% of total subjects in dataset) African American Heritage Asian Heritage American Indian/Alaskan native Heritage (mainly subjects recruited in Peru) Multiple (mainly subjects recruited in Brazil)	 2 (1.2%) 41 (24.7%) 87 (52.4%) 36 (21.7%)

Source: Applicant's population PK report (Study 2017n331946 Report), Page 17, Table 3

METHODS

The population PK analysis was performed using NONMEM software, Version 7.3.0 (ICON Development Solutions) and run management was performed using Pirana (version 2.9.0) on the Model-based Analysis Platform (MAP). All data preparation, summary statistics (mean, median, standard deviation, and other measures, as appropriate), and presentation were performed using validated SAS® software (version 9.2 or higher) and/or R© (version 3.3.2) with RStudio© (version 0.99.902). Simulation datasets were generated with dense PK sampling time points while maintaining all the demographics and study design characteristics as in the original analyses data file.

Ninety pre-dose concentrations from healthy volunteer studies had no quantifiable concentrations and were excluded from the analysis. 3.74% of observed concentrations data were below quantification limit (BQL) or non-quantifiable (NQ) and were excluded from the PopPK analysis.

A 2-compartment structural model was utilized as a starting point for further analysis. Log transformation on concentrations were utilized for model building to provide model stability in this PopPK exercise with TQ concentrations ranging from 2.13 to 1013.25 ng/mL. Covariates were evaluated in this PopPK analysis to assess the impact of key demographics, formulation, and other relevant variables on drug exposure in subjects. Forward inclusion of relevant covariates was determined by a reduction in the OBJFV of 6.64, for a Chi squire (χ^2) significance of < 0.01 for 1 degree of freedom (df) using FOCE-I. After the full model was defined, the significance of each covariate was tested individually by removal one at a time from the full model. A covariate was retained in the model if, upon removal, the OBJFV increases by more than 3.8 points (χ^2<0.05 for 1 df)) using FOCE-I. Model performance for the final PopPK TQ model was conducted using the following several approaches:

1) Bootstrapping: the analyses data were sampled with replacement at subject level to generate 500 datasets. The final PopPK model was then bootstrapped with these 500 datasets. Median parameter estimates and 90% confidence intervals were calculated and compared with those obtained from the final model.
2) Visual predictive checks (VPCs): VPCs were performed with 500 replications by using the base and final population PK model parameters to compare the distribution of simulated population PK data (median, 95% confidence interval) to the observed data. The VPC of the final model was performed using parameter estimates from the bootstrap runs. The VPCs were also stratified by study, doses and other key covariates of relevance (e.g., formulation, race, health status).
3) External dataset: 500 clinical trials were simulated using 500 vectors of bootstrap parameter estimates from the final PopPK model with a simulation dataset comprising of TAF116564 study subject demographics using the mrgsolve package in R. The median and 95% prediction intervals from these simulations were overlaid with the observed data from the TAF116564 study dataset to assess model performance in predicting the concordance with TQ concentrations from TAF116564 study.

Relative Bioavailability across Formulations

The final PopPK model was utilized to characterize any differences in relative bioavailability across formulations utilizing the approaches as below:

1) The relative bioavailability population parameter (F1) of formulations was estimated from the final PopPK model in the NONMEM analysis. The parameter point estimate and precision around the estimate was obtained by bootstrap approach.
2) For the second approach, the exposures were computed via the individual *post-hoc* PK parameters obtained from the final PopPK model and compared across TAF112582 part I (capsule formulation), part II (tablet formulation) and TAF116564 (tablet formulation) studies.
3) For the third approach, predicted exposures obtained from the 500 bootstrap estimates were compared between TAF112582 part 1 (capsule formulation), part 2 (tablet formulation) and TAF116564 (tablet formulation) studies.

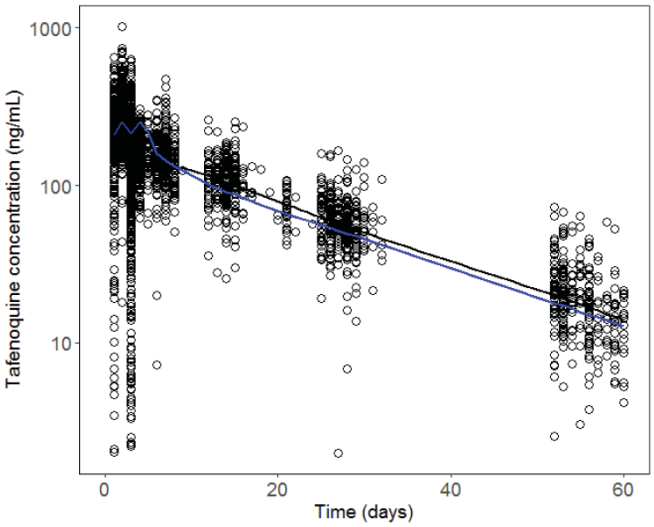
Reviewer's comments: The review team agrees that the approach 1) as mentioned above by the Applicant can be used as an appropriate method to assess the relative bioavailability between tablet and capsule. However, both approaches 2) and 3) are based on the predicted exposures across studies and may have a higher risk of providing biased estimate of the formulation effect on absorption. Therefore, approaches 2) and 3) are not appropriate for bioavailability assessment but can provide post-hoc estimate of exposures for Phase 2 and Phase 3 studies.

RESULTS

Population PK model

The base model was a two-compartment model with first order absorption and elimination (taf214B). TQ concentration-time profile and the fitting of the base model to the observed TQ data from all 5 studies is shown in **Figure 1**.

Figure 1 TQ concentration vs time for 300 mg dose



The circles represent the observed data and the black line is the loess curve for the observed data up to day 60. The blue line represents the population predicted concentrations (PRED) from the model taf214B.

Source: Applicant's population PK report (Study 2017n331946 Report), Page 17, Figure 1

The final model (taf218P3) was a two-compartment model with allometrically scaled weight as a covariate on CL/F, V2/F, Q/F and V3/F; formulation status as a covariate on F1 and KA1; and Health status as a covariate on V2/F and V3/F. The parameter estimates from that model are listed in Table 4. The goodness of fit plots from this final mode are presented in **Figure 2**.

Table 4. Population PK parameters for the final model (Model taf218P3) and bootstrap results

	Final model Parameters	Bootstrap Results[3]	
Parameter	Model Estimate	Median Estimate	90% CI
CL/F (L/h)	2.96	2.96	2.87-3.05
V_2/F (L)	915.00	912.94	878.67-956.19
Q/F (L/h)	5.09	5.10	4.76-5.43
V_3/F (L)	664.00	665.39	634.00-691.60
ALAG1 (hours)	0.91	0.93	0.90-0.95
K_{A1} (hours^{-1})	0.25	0.25	0.23-0.29
Formulation$_{CAP}$ on K_{A1}	0.92	0.92	0.81-1.03
Formulation$_{CAP}$ on F1	0.86	0.86	0.83-0.90
Health status$_{incr}$ on V_2	1.35	1.35	1.30-1.41
Health status$_{diff}$ on V_3	0.347	0.340	0.30-0.40
IIV[1] CL/F	32.10	31.97	30.00-34.13
IIV V_2/F	34.40	34.25	31.79- -37.11
IIV[2] CL-V_2 Block	33.30	29.92	27.65 -32.47
IIV K_{A1}	40.40	39.63	31.71-48.00
IIV ALAG1	44.30	43. 35	38.82-56.14
IIV error	33.00	33.17	27.17-38.47
Random Residual Variability (% CV)	15.00	14.94	14.25-15.78

[1]Interindividual variability (IIV) expressed as % coefficient of variation
[2]Covariance between CL/F and V_2/F
[3]Bootstrap based on 500 runs
K_{A1}: absorption rate constant; CL/F: oral clearance from first (central) compartment; V_2/F: distribution volume of first (central) compartment; V_3/F: distribution volume of second (peripheral) compartment; Q/F: inter-compartmental clearance; F: bioavailability
Allometric scaling for PK parameters was applied as described below:
CL/F (L/h)= $2.96*(WT/70)^{0.75}$; V2/F (L)= $915*(WT/70)^{1}*1.35$(Healthy); Q/F (L/h)= $5.09*(WT/70)^{0.75}$; V3/F (L)= $664*(WT/70)^{1}*0.347$(Healthy); F1cap=0.86*1; KAcap=0.92* KAtab

Source: Applicant's population PK report (Study 2017n331946 Report), Page 35, Table 6

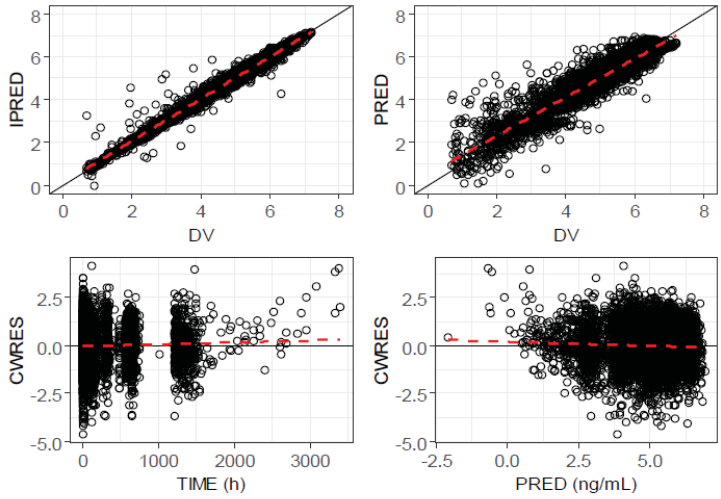
Model Performance

The final model (taf218P3) was verified by the following approaches.

Diagnostic Plots

The goodness of fit plots from this final mode are presented in **Figure 2**.

Figure 2. Goodness of fit plots for the final model (taf218P3)



The circles represent the observed data (DV), individual predictions (IPRED), population predictions (PRED) and conditional weighted residuals (CWRES). The solid line represents the line of unity and the dashed red line represents the trend line for the corresponding data.

Source: Applicant's population PK report (Study 2017n331946 Report), Page 36, Figure 12

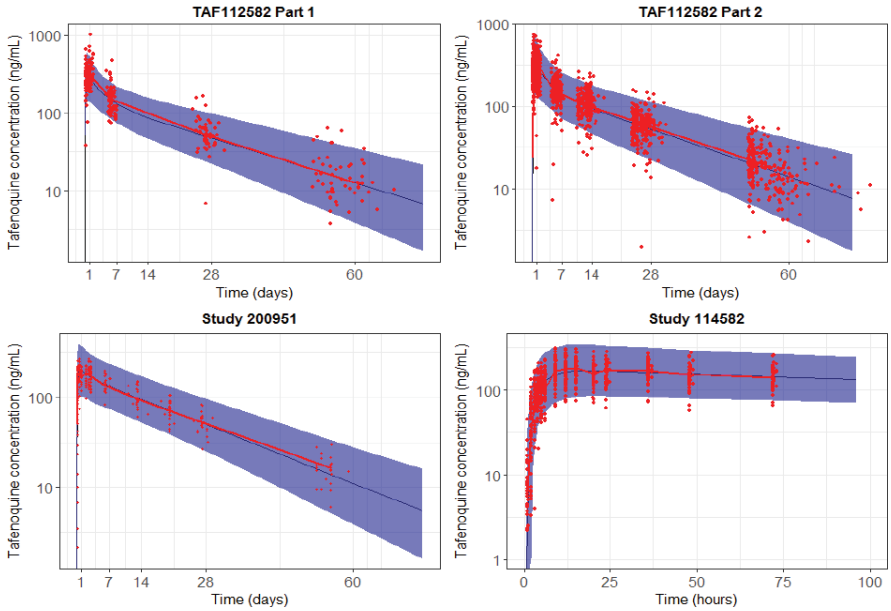
Bootstrapping

The parameter estimates were generated for the final model taf218P3 based on 500 datasets that were generated by sampling (with replacement) subject level data. The median and 90% CIs of the parameter estimates from the bootstrap run were compared with estimates from a single model run (final model taf218P3) and are listed in **Table 4**. The population PK parameters estimated from the final model are close to the median estimates from bootstrapping and within the 90% CI of bootstrap results (**Table 4**).

Visual Predictive Checks

Example VPCs for some studies and doses are presented below in Figure 3. The model predictions appear to capture the observed concentration time points and trends across different doses, studies and populations (Healthy and Patients) within the 2.5th and 97.5th percentiles of the simulated values.

Figure 3. Model 218P3 (final model) VPC plot by study for 300 mg dose



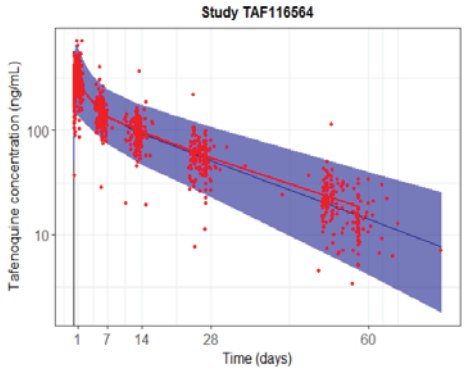
The blue bands and lines represent the 95 percent prediction intervals and median prediction, respectively. The red dots and red line represent the observed data and observed median, respectively.

Source: Applicant's population PK report (Study 2017n331946 Report), Page 39, Figure 14

External validation

The final model (taf218P3) was utilized to simulate TQ concentrations in a study population reflecting the TAF116564 study demographics. 500 clinical trials were simulated using bootstrap parameter estimates with a simulation dataset comprising of TAF116564 study subjects and a dense sampling grid. **Figure 4** shows the VPC from the simulation which demonstrated agreement with TQ concentration-time profiles from TAF116564 study systemic exposure well.

Figure 4. Model 218P3 VPC plot for TAF116564 Study



The blue bands and lines represent the 95 percent prediction intervals and median prediction, respectively. The red dots and red line represent the observed data and observed median, respectively.

Source: Applicant's population PK report (Study 2017n331946 Report), Page 40, Figure 15

Reviewer's comments: The final PopPK model is acceptable. The model diagnostics showed that the observed PK data can be adequately described by the model.

Covariate Evaluation

Selection of key covariates was based on physiological relevance, understanding the key differences across populations and studies. Notable differences across studies are the health status (patients vs healthy volunteers) and formulations used (tablets vs capsules). Consequently, exploratory covariates vs ETA plots were generated to evaluate any bias across these and other covariates. Several key covariates were evaluated with the structural 2 compartment model and are described below. Table 5 provides a summary of the key models that were evaluated to arrive at the final model.

Table 5. Key population PK models for parameter evaluation

MAP Model #	Model	Minimum Objective Function Value (OBJFV)	Change in OBJFV[1]	Comments
taf214B	2 compartment model	-7749.997	-	Starting point based on TAF112582 part 1
taf215	taf214B + WT on CL/F, V_2/F, Q/F, V_3/F	-7803.266	-53.269	Base Model: Significant drop in OBJFV. Weight was retained in the model
taf218	taf215+ Formulation on F1	-7925.815	-122.549	Significant drop in OBJFV; explains the relative bioavailability between the tablet and capsule formulations. Formulation retained in model
taf218A	taf218+ Formulation on KA1	-7933.179	-7.364	Significant drop in OBJFV. Formulation on KA1 retained in model
taf218P	taf218A+IIV on ALAG1	-9182.453	-1195.274	Significant drop in OBJFV. Improved fit for the earlier time points. Retained in the model.
taf218P1	taf218P+Health status on V_2	-9237.692	-109.239	Significant drop in OBJFV. Improved fits for early time points of healthy volunteer studies. Retained in the model
taf218P3	taf218P1+Health status on V_3	-9468.988	-231.296	Final model: Significant drop in OBJFV. Improved fits for distribution phase of healthy volunteer studies. Retained in
Backward elimination				
taf218P3_bw1	taf218P3- Health status on V_2	-9391.797	77.191	Significant increase in OBJFV. Health status on V_2 retained in the model
taf218P3_bw2	taf218P3- Formulation on F1	-9424.061	44.927	Significant increase in OBJFV. Formulation on F1 in the model
taf218P3_bw3	taf218P3- Formulation on KA1	-9489.369	-20.381	Although a drop in OBJFV, negligible change in the model parameters. Formulation related KA retained in the model to better characterize the absorption profiles between the two formulations
taf218P3_bw4	taf218P3-Healthy on V_3	-9243.146	225.842	Significant increase in OBJFV. Health status on V_3 retained in the model

[1]Change in Objective Function Value (OBJFV) compared to the previous model.

Effect of Formulation status

Capsule was used in the TQ clinical studies until Phase 2B and tablet was utilized in the Phase 3 studies and other Phase 1 studies conducted alongside the Phase 3 studies. Formulation was identified as a statistically significant predictor of the inter-individual variability (IIV) in TQ relative bioavailability (F1) and rate constant of absorption (Ka).

The drug formulation was introduced as a covariate on the bioavailability term F1 in the model with the tablet (intended to-be-marketed formulation) as the reference (i.e., $F1_{tablet}$=1). The relative bioavailability of capsules was 83.3% of the bioavailability of tablets (i.e., 1-0.833=0.167 or 16.7% less than tablets) based on the model taf218. While the difference in bioavailability point estimate between these two formulations based on this model was less than 20%, the covariate was retained in the model to get a more granular assessment of any exposures differences that may arise from these different formulations.

A separate formulation specific absorption rate (KA) was characterized for the capsules as a fraction of tablet's absorption rate to capture any differences in the Cmax between formulations. The point estimates indicated that the $KA_{capsule}$ for capsules was 83.5% of that of tablets. During the backward elimination step, the OBJFV dropped by eliminating impact of formulation on absorption rate constant (KA), there were negligible changes in the PopPK parameter estimates. However, considering that formulation specific KA allowed closer approximation of Cmax, formulation specific KA was also retained in the final model.

Relative Bioavailability across Formulations

Based on the final model taf218P3, the relative bioavailability point estimate of capsules was estimated to be 86% (F1capsules=0.86) as compared to that of tablets. In other words, tablets have approximately 14% lower exposures in capsules compared to the tablet formulation. The 90% confidence interval on the relative bioavailability estimate for capsules (F1capsules) from the 500 bootstrap runs was 0.83-0.90.

Reviewer's Comments: Based on the final population PK model, the relative bioavailability [mean (90% interval)] of tablet is estimated to be [116% (111-120)] of capsule. Based on the available data, we agreed that there was no strong evidence suggesting that TQ exposures would be significantly different between the tablet formulation and capsule formulation.

Effect of Health status

Health status was identified as a statistically significant predictor of the IIV in TQ volume of distribution in central compartment (V2) and in peripheral compartment (V3). In Model 218P1, health status was added as a covariate on V2 and it was modelled as a fraction of apparent volume of distribution in patients. The model demonstrated that healthy subjects had approximately 30% higher V2 (HealthV2=1.3), compared to the malaria patients.

To account for any differences in the volume of distribution in the peripheral compartment, health status was applied as a covariate for the apparent peripheral volume of distribution (V3). The model demonstrated that healthy subjects had a lower volume of distribution in the peripheral compartment (V3) which is approximately 35% of that from the malaria patients.

The covariate analysis showed that patients have a lower apparent central volume of distribution as compared to healthy subjects. The higher volume of distribution (post covariate addition) in healthy volunteers resulted in lower early concentrations in line with observed data. The Applicant proposed the following reasons that contribute to the difference in central volume of distribution between the healthy subjects and patients: (1) The higher concentrations in patients (lower volume of distribution) as compared to healthy volunteers may be due to CQ background therapy. A previous DDI study with CQ in healthy volunteers (TAF106491) showed that TQ exposures, Cmax and AUC(0-24h), increased by 38% and 24%, respectively, when TQ was co-administered with CQ. Patients with *P. vivax* malaria that provided PK data in this population PK analysis all received CQ as background medication (i.e., studies TAF112582 Part 1/Part 2 and TAF116564) and may demonstrate a higher Cmax than the

healthy subjects; (2) Subjects with malaria infection may be suffering from varying levels of dehydration thus having lower volume of distribution as compared to healthy volunteers.

The model also identified that patients have a higher apparent peripheral volume of distribution as compared to healthy subjects. The Applicant hypothesized that malaria infection upsets the basement membrane or cell-cell interactions resulting in a "leakier" environment for drug distribution which may reflect as a higher V3 in patient population.

Effect of Body Weight

Body weight has been identified to be a statistically significant predictor of the IIV in TQ volume distribution in a previously developed population PK model based on data from Study TAF112582 Part 1. In this study, allometric weight-based scaling was applied to all clearance and volume PK parameters (CL/F, V2/F, Q/F and V3/F) as a physiologically relevant approach. Inclusion of weight in the model led to a significant drop in the objective function value (OBJFV). This approach will also be helpful for broader application of this model across other populations (e.g., characterizing pediatric exposure). Hence, the Applicant used the model with body weight as covariate on all clearance and volume PK parameters (taf215) as the base model and applied this model for all further analysis.

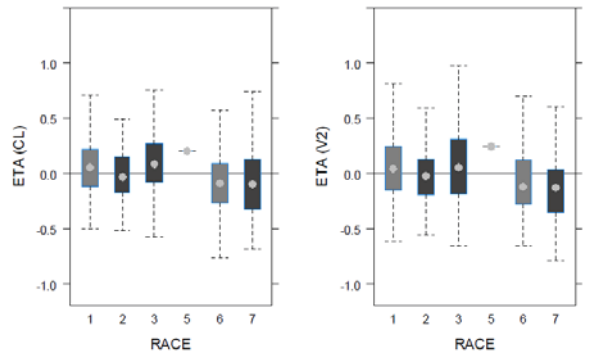
Reviewer's Comments: The Applicant incorporated body weight as a covariate in the final PopPK model mainly to characterize the allometric scaling of PK parameter based on body weight for the future use in pediatric patients. Body weight is not expected to impact PK parameter in adults to the level that dose adjustment is warranted.

Effect of Race

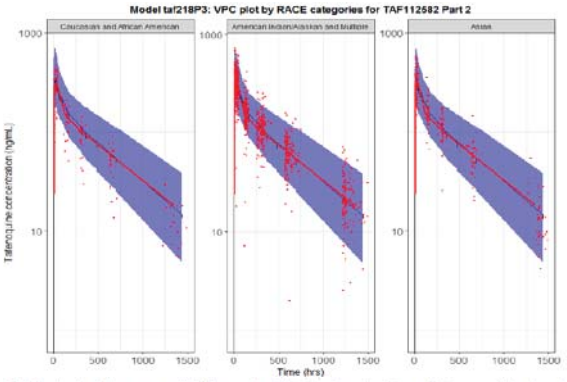
Race was not a statistically significant predictor of the IIV in TQ PK. There was a slight deviation in the diagnostic ETA plots for RACE, especially for two key races - Alaskan Indian/Native American and Multiple, as shown in **Figure 5**. However, this may be due to the PK difference between healthy subjects and patients since these races are predominantly present only in the patient studies. VPCs were generated from the previous model taf218P3 and demonstrated adequate model performance for these races. Thus, addition of race was not warranted in the PopPK model.

Figure 5. ETA CL and V2 plots vs RACE for the model 218P3 (A) and VPC plot of TQ 300 mg dose for model 218P3 by Race in representative TAF112582 Part 2 Study (B)

(A) (B)



Race codes and number of subjects per race are outlined as 1= Caucasian race, N= 95 (14.1%); 2=African American race, N=123 (18.2%); 3=Oriental or Asian race, N=160 (23.7%); 5=Other, N= 1 (0.1%); 6= American Indian or Alaska native race, N=193 (28.6%); 7= Multiple, N= 103 (15.3%)



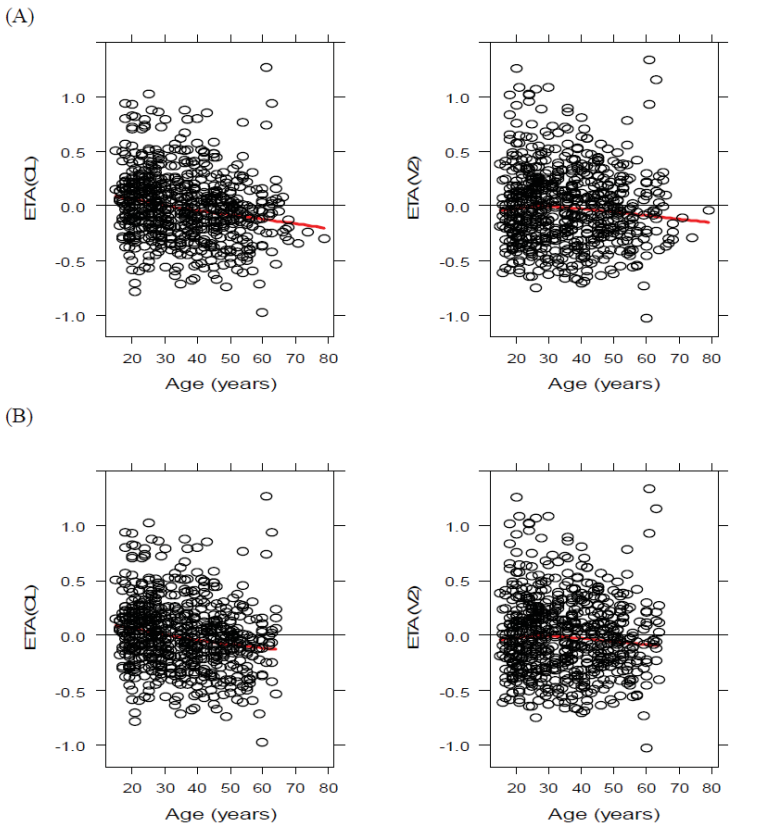
The blue bands and lines represent the 95 percent prediction intervals and median prediction, respectively. The red dots and red line represent the observed data and observed median, respectively. For TAF112582 Part 2 study, Caucasian race (4, 1.5%) and African American race (28, 10.8%); American Indian/Alaskan and Multiple (80, 30.9%) and Multiple (97, 37.5%) and Oriental or Asian race (50, 19.3%).

Source: Applicant's population PK report (Study 2017n331946 Report), Page 29, Figure 9 for (A) and Page 30, Figure 10 (A) for (B)

Effect of AGE

Age was not a statistically significant predictor of the IIV in TQ PK. The diagnostic ETA plots from the model taf218p3 showed a slight trend of deviation from the line of unity in the higher age range (**Figure 6A**). On closer examination, this trend was driven primarily by subjects greater than 65 years of age (N=13 out of 675 subjects, i.e., < 2% of the data). ETA plots without these subjects demonstrated no trend as seen in **Figure 6B**. In general, over the current age range studied in TQ clinical studies, there is no relevant impact of AGE on TQ PK.

Figure 6. Final model (218P3) ETA plots by AGE for (A) all subjects and (B) excluding subjects >65 years of AGE



The circles represent the ETA (CL) and ETA (V_2) for each subject using the final model taf218P3. The solid line represents the line of unity and the dashed red line represents the trend line for the corresponding data.

Source: Applicant's population PK report (Study 2017n331946 Report), Page 32, Figure 11

Predicted TQ exposures based on post-hoc estimated PK parameters

The final model using the bootstrap median estimates was used to fit the observed data from Phase 2 dose ranging study (TAF112582 part 1) and Phase 3 studies (TAF112582 part 2 and TAF116564) to obtain the *post-hoc* individual PK parameters (CL, V2, Q, V3, F1 and ALAG1). A new population with the similar demographics (as that of the estimation and validation dataset) and intense sampling times was created and merged with the individual *post-hoc* PK parameter estimates for those subjects obtained. The corresponding IPREDs obtained were used to compute the AUC0-t and Cmax values for the 300 mg doses across the studies. The predicted TQ exposures obtained from the post-hoc PK parameters are summarized in **Table 6**.

Table 6. Summary of TQ exposures obtained using post-hoc PK parameter estimates

Study	Formulation	Dose (mg)	AUC_{0-60} (ug*h/mL) Median (5th-95th percentile)	C_{max} (ng/mL) Median (5th-95th percentile)
DETECTIVE Part I	Capsule	300	93.58 (62.30-152.36)	334.76 (187.99-549.11)
DETECTIVE Part II	Tablet	300	104.38 (61.05-151.76)	330.07 (193.06-504.93)
GATHER	Tablet	300	96.12 (62.31-135.26)	301.82 (179.15-428.09)

AUC_{0-60} summarized the AUC up to day 60

DETECTIVE is referred to TAF112582; GATHER is referred to TAF116564

Source: Applicant's population PK report (Study 2017n331946 Report), Page 41, Table 7

REVIEWER'S ASSESSMENT

The results of TQ PopPK analysis showed that a two-compartment model including body weight (allometric scaling) on CL/F, V2/F, Q/F and V3/F, Formulation on F1, KA and Health status on V2/F and V3/F reasonably described the PK data.

The PopPK model was used to characterize relative bioavailability across formulations to assess any exposure differences between capsules administered to patients in the phase 2b dose ranging study vs tablets administered to patients in Phase 3 pivotal and safety studies. After adjusting other covariates, the final POP PK model showed that the relative bioavailability of tablets is 116% (111-120%) [median (90% CI)] compared to that of capsules, which is considered to have no clinically relevant impact on TQ exposure.

15.4.3.Exposure-Response Analyses

The exposure-response (E-R) analysis for TQ was conducted by the applicant using a logistic regression analysis in subjects with *P. vivax* malaria solely based on pharmacokinetic (PK) and pharmacodynamic (PD) data from Study TAF112582 Part 1. Five PK samples were collected; two from time windows of 4h to 8h and 24h to 48h post-dose and three from Days 8, 29 and 60. The AUC of each subject was calculated based on the individual oral clearance (CL/F) using the equation of "AUC=Dose/(CL/F)". The individual oral clearance was derived from final population PK model for TQ. The efficacy endpoint was probability of being recurrence-free of *P. vivax* malaria (1 = recurrence-free, 0 = recurrence) at the 6-month time point in subjects who received TQ. A total of 164 subjects were included in the ER analysis, with 52 subjects who were recurrence in 6-month after initial clearance and 112 subjects who were recurrence-free at the 6-month assessment. Other than these 164 subjects, the E-R analysis did not include data from Indian as the 6-month recurrence rates in India were very low. The 6-month recurrence rates were also high in subjects treated with CQ only (which has no anti-recurrence efficacy). Only subjects with efficacy information at 6 months were included in the E-R analysis. Therefore, patients who were not parasitemic or having no confirmed parasite assessment at month 6 were excluded from the E-R analysis.
The demographics of subjects included in E-R analysis is shown in Table 1.

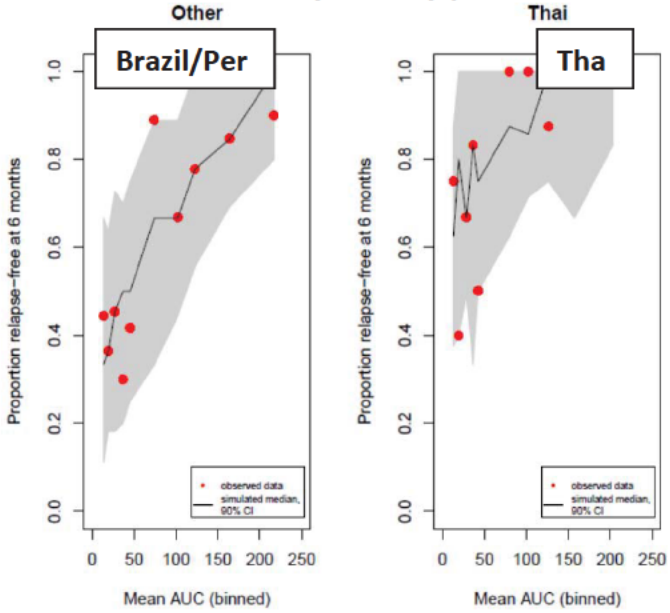
Table 1 Summary of the Demographics of Subjects Included in the E-R Analysis (6 months)

Demographic	Mean (SD)	Median (Range)
Age (Years)	35.7 (14.1)	35 (16-74)
Weight (kg)	60.5 (12.0)	59.0 (37.2-106.0)
BMI (kg/m^2)	23.7 (4.5)	22.9 (16.8-39.2)
	Category	**Number (%)**
Gender	Male	126 (77)
	Female	38 (23)
Baseline parasitemia count	≤ 7500/µL	117 (70)
	> 7500/µL	47 (30)
Country	Brazil	24 (15)
	Peru	79 (48)
	Thailand	61 (37)
Dose	50 mg	40 (24.4)
	100 mg	43 (26.2)
	300 mg	44 (26.8)
	600 mg	37 (22.6)

Source: Applicant's E-R report, Page 7, Table 3
The logistic regression analysis showed that AUC and country (Thailand compared to Brazil/Peru) were significant covariates for probability of being recurrence-free at 6 months. Weight was not associated with probability of being recurrence-free at 6 months after adding AUC and country. The final model was evaluated graphically by a visual predictive check (VPC).

Simulation with the final model indicated that the model described the relationship between AUC and country and the probability of being recurrence-free at 6 months.

Figure 1 Simulated Versus Observed Proportion of Subjects Receiving TQ who are Recurrence–Free at 6 Months by Country (Thailand and Brazil/Peru)



Source: Applicant's E-R report, Page 12, Figure 3b.

Parameter estimates for the final model for the E-R analysis of probability of being recurrence-free at 6 months are shown in Table 2.

Table 2 Parameter Estimates for the Logistic Regression analysis

Parameter	Population Mean (% CV)[a]
intercept	0.13 (172)
slope (AUC)	0.0164 (23.6)
beta (country)	1.27 (32.7)

a. precision expressed as % coefficient of variation
Source: Applicant's E-R report, Page 13, Table 4.

E-R analysis was also conducted using a time-to-event approach where time to recurrent malaria was coded as an event and subjects with no recurrent malaria were censored. A total of 180 subjects were included in the time-to-event analysis with 51 subjects relapsed and 129 subjects censored. For subjects who took an anti-malaria drug and were not parasitemic (N=10) and subjects without confirmed parasite-free at the 6-month assessment (N=7) as shown in Table below, they were treated as censored subjects at the day of last valid assessment available.

Table 3 Summary of the Subjects Included in the Time to Event PK/PD Analysis

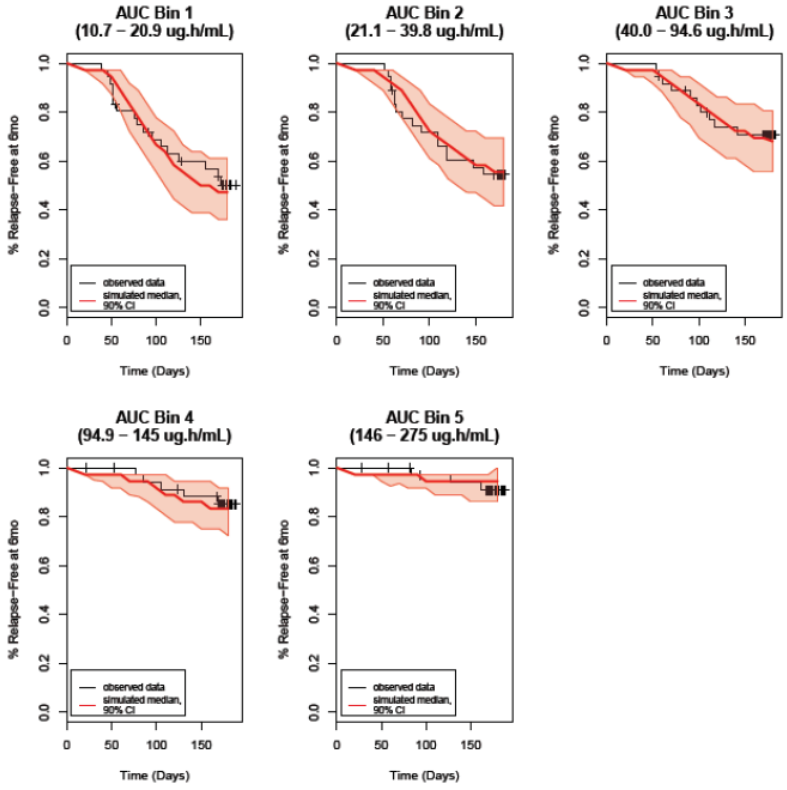
	Status	Code*	Number
Relapse (Event)	1	1	51
Relapse-free (Censored)	0	2	112
		5	10
		6	7
			129 (total)
	Median (range)		
Time of initial parasite clearance (day)	2 (1 – 6)		
Time of relapse (day)	86 (38 – 172)		

a. Code: 1 = relapse; 2 = no relapse at 6 month assessment; 5 = took an anti-malarial drug and were not parasitaemic; 6 = not confirmed parasite-free at the 6 month assessment

Source: Applicant's E-R report, Page 18, Table 8

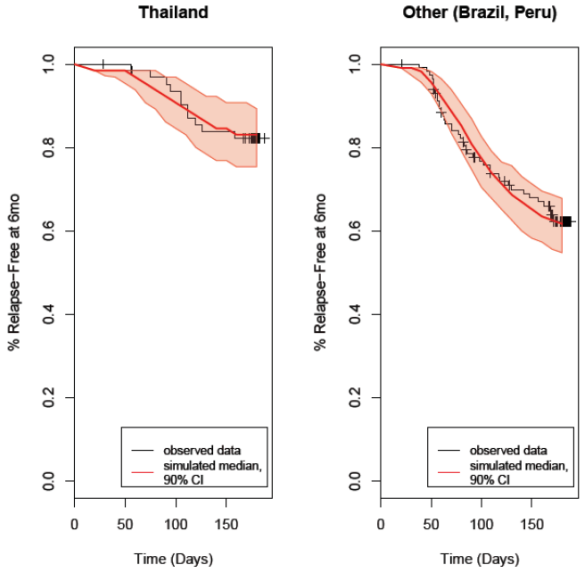
A Weibull distribution hazard model with the addition of the delay function ($e^{(-a*time)}$) was used in the analysis. Based on the multivariate analysis, AUC and country (Thailand compared to Brazil/Peru) were significant covariates. Weight was not a significant covariate. Simulation with the final model indicated that the model described the survival probability (recurrence-free status) over time (Figures 2 and 3).

Figure 2 Survival Plot (Recurrence-Free Status) for Subjects Receiving TQ by AUC bin



Source: Applicant's E-R report, Page 19, Figure 5a.

Figure 3 Survival Plot (Recurrence-Free Status) for Subjects Receiving TQ by Country



Source: Applicant's E-R report, Page 20, Figure 5b.

The final parameter estimates are shown in Table 4.

Table 4 Population Parameter estimates for Subjects Receiving TQ in the Time-to-Event Analysis

Parameter	Population Mean (% CV)[a]
base	1.69 e-9 (43.7)
shape	5.06 (4.2)
delay function	0.045 (13.3)
slope (AUC)	-0.0144 (24.4)
beta (country)	-1.01 (32.9)

Source: Applicant's E-R report, Page 21, Table 9.

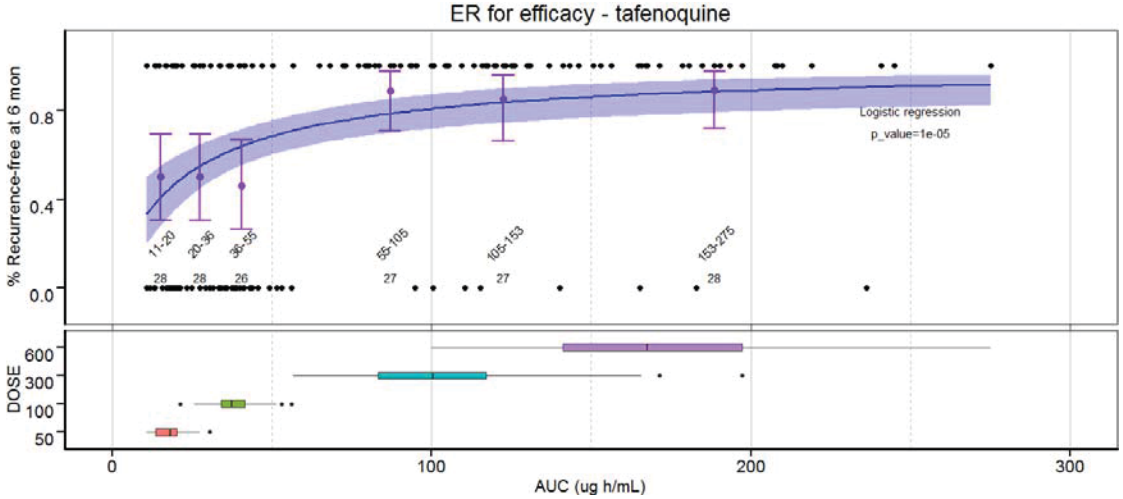
Reviewer's comments: The dose-response relationship using recurrence-free rate at 6 months shows that both 300 and 600 mg doses were associated with high response rate (Table 5). Although the recurrence-free rate at the month 6 differed among regions (Thailand, Brazil/Peru, and India), the recurrence-free rate appears to plateau at 300 mg regardless of region. Little efficacy improvement can be seen for the dose of 600 mg compared to 300 mg.

Table 5 Recurrence-free at six month (Kaplan-Meier Methodology)

Dose	*Placebo*	*50 mg*	*100 mg*	*300 mg*	*600 mg*
% Recurrence-free at 6 mon (Kaplan Meier)	*37.5% (N=54)*	*57.7% (N=55)*	*54.1% (N=57)*	*89.2% (N=57)*	*91.7% (N=56)*
By Country					
% Recurrence-free at 6 mon (Kaplan Meier), Brazil	*16.7% (N=6)*	*33.3% (N=6)*	*33.3% (N=6)*	*83.3% (N=6)*	*85.7% (N=7)*
% Recurrence-free at 6 mon (Kaplan Meier), Peru	*12.2% (N=22)*	*45.5% (N=22)*	*39.5% (N=24)*	*81.1% (N=23)*	*84.0% (N=23)*
% Recurrence-free at 6 mon (Kaplan Meier), Thailand	*56.3% (N=16)*	*60.0% (N=16)*	*67.3% (N=16)*	*94.7% (N=19)*	*100% (N=16)*
% Recurrence-free at 6 mon (Kaplan Meier), India	*90.0% (N=10)*	*90.9% (N=11)*	*80.0% (N=11)*	*100% (N=9)*	*100% (N=10)*

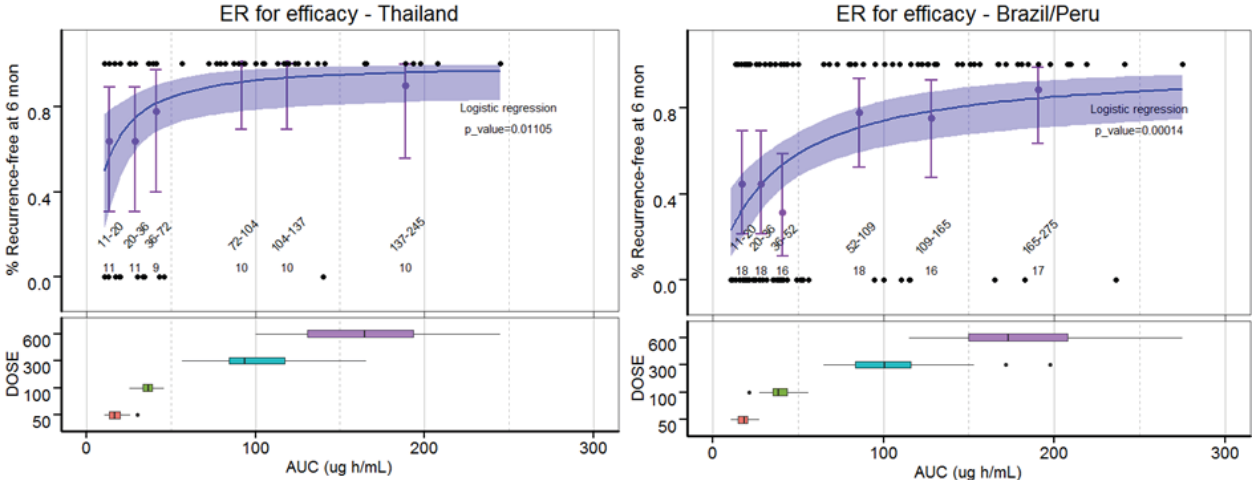
Source: Applicant's study report for TAF112582 Part 1, Page 87 and 94-95, Table 22, Table 32-34
Base on dose-response relationship, a model with saturable instead of linear structure should be used for exposure-response analysis. The Reviewer conducted an independent exposure-response analysis using the data from Study TAF112582 Part 1 by excluding Indian patients due to high response rate. The results are shown in Figure 4.

Figure 4 Exposure-response relationship for recurrence-free rate at 6 month



Source: Reviewer's independent analysis
The plot shows that the exposure following doses less than 300 mg (50 and 100 mg) was associated with a relative low response rate while the exposure following doses of 300 mg and 600 mg was associated with comparable high response rate. The result confirmed that the recurrence-free rate at 6 months is saturated with a dose of 300 mg or higher.
The exposure-response analysis for recurrence-free rate at 6 months was further conducted by country. A similar result can be seen.

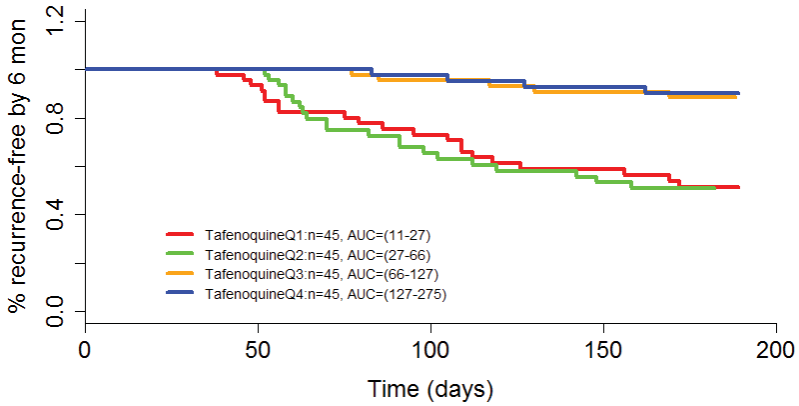
Figure 4 Exposure-response relationship for recurrence-free rate at 6 month by country



Source: Reviewer's independent analysis

A time-to-event analysis was performed and result is shown in Figure 6. The result is consistent with that from exposure-response analysis for recurrence-free rate at 6 months.

Figure 6 Time to event analysis for recurrence-free at 6 months



Source: Reviewer's independent analysis

15.4.4.Pharmacogenomics Review

Background
Glucose-6-phosphate dehydrogenase (G6PD) provides the only source of reduced nicotinamide adenine dinucleotide phosphate (NADPH) in erythrocytes as it catalyzes the conversion of glucose-6-phosphate into phosphogluconolactone (Chang et al.). NADPH is essential in maintaining the redox state of erythrocytes and protecting them from oxidative stress and subsequent hemolysis (Capellini et al.). Erythrocytes deficient in G6PD are susceptible to hemolysis under oxidative stress presented either by endogenous or exogenous oxidative compounds such as 8-aminoquiniline-based drugs (von Seidlein et al.).

G6PD deficiency
G6PD deficiency is a result of genetic polymorphisms in *G6PD*, the gene that codes for G6PD. These polymorphisms result in variants that impact G6PD activity largely through impacting its stability. Polymorphisms in the X-linked *G6PD* produces a population of hemizygous males, homozygous females, and heterozygous females who carry two distinct populations of erythrocytes arising from each allele that result in variable levels of enzyme activity. The global prevalence of G6PD- deficiency is estimated to be 4.9% with prevalence estimates ranging from 2.9% in Pacific populations to 7.5% in African populations (Nkhoma et al.).
Correlating genetic variants to phenotypes have historically been mediated by the level of enzyme activity and the clinical presentation of the carrier. Five *G6PD* variant classes were introduced by the world health organization (WHO), three of which are deficient categories (WHO working Group). Class I variants present as a severe deficiency with chronic hemolysis, class II variants present as a severe deficiency with intermittent hemolysis, and class III variants present as a mild to moderately deficient phenotype. The WHO classification defines enzyme activities between 60-150 % of normal enzyme activity as normal functional status, mild to moderate deficiency as 10 -60% of normal enzyme activity and severe deficiency as < 10% normal enzyme activity (WHO Working Group). 100% enzyme activity is derived from an adjusted quantitative (amount of hemoglobin IU/gHb or number of cells U/10^{12} RBC) median of all male samples from a defined sample set (Ley et al.) given that enzyme activity in their erythrocytes reflect the only copy of *G6PD* they carry.

Testing for G6PD deficiency

The G6PD testing platforms include qualitative tests that provide a binomial normal or deficient outcome, quantitative tests that measure G6PD activity in a red blood cell population, genetic tests to determine G6PD variants, and cytochemical tests that provide a measure of mosaicism in the erythrocytes of heterozygous females. Notably, determining the risk for hemolysis in heterozygote females is not possible without measuring G6PD activity. The WHO enzyme activity thresholds are extensively referenced in G6PD literature (Capellini et al., Relling et al., Frank, Domingo et al.) however, ambiguity in how normal G6PD activity is determined in practice and the inconsistencies in boundaries (ranging from 10 to 30% of normal enzyme

activity) for defining normal and deficient activity across qualitative test platforms have elicited calls for standardization (Domingo et al.).

Applicant analysis

Phase 1 assessment of hemolytic potential of TQ (TQ) in healthy volunteers (study TAF110027)

The applicant compared G6PD-deficient heterozygous females (WHO-class III variant) to G6PD-normal subjects in an open-label, single-dose, dose-escalation study.

Summary of subjects in TAF110027

Table1: Summary of subjects enrolled in dose-escalation phase of Study TAF110027

Cohort	G6PD-deficient with WHO class III variant (40- 60% enzyme activity of median site normal)	G6PD-normal: > 80% enzyme activity of median site normal
100 mg TQ*	6	6
200 mg TQ	6	6
300 mg TQ	3	6
15 mg PQ (PQ) daily x 14 days	5	6

Source: NDA 210795 study report trial TAF110027

* Both 100 mg cohorts were recruited using cytochemical staining that exhibited variable and non-reproducible results. Subsequent cohorts were enrolled using a quantitative assay with a locally defined median as benchmark for 100% normal activity as determined in study *TAF115016*

After determining 200mg TQ as the highest non-hemolytic dose, the applicant assessed the hemolytic potential of single dose of 200 mg TQ in an additional cohort of G6PD-deficient heterozygous females with 61-80% and >80% enzyme activity of site median normal value.

Table2: Summary of subjects enrolled in the additional cohort of Study TAF110027

	Number of subjects with % enzyme activity of median site normal	
Cohort	61- 80%	> 80%
Single TQ 200 mg dose	2	5

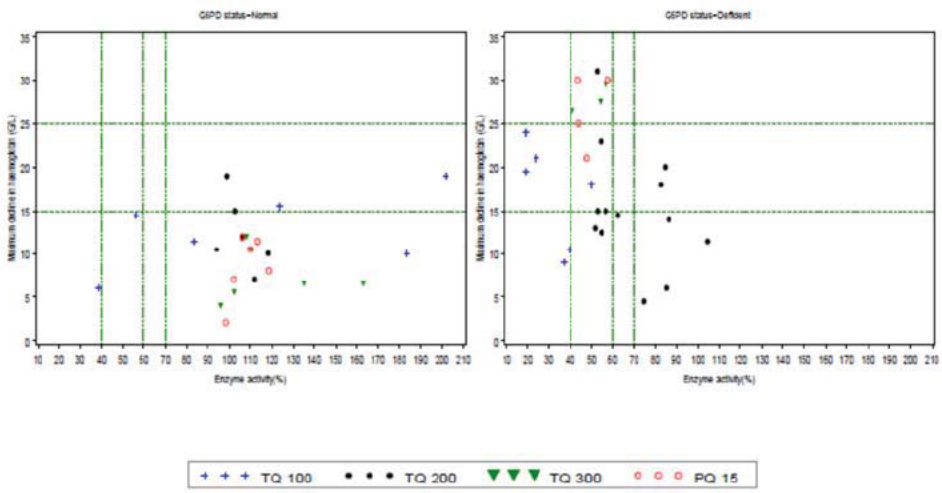
Source: NDA 210795 study report trial TAF110027

The primary endpoint was maximum absolute decline in hemoglobin from baseline in G6PD-deficient heterozygous healthy volunteers with varying degrees of G6PD enzyme activity compared to G6PD-normal.

The applicant reported determining G6PD genotype status using Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP). G6PD deficiency diagnosis was confirmed using a quantitative G6PD enzyme assay. All deficient subjects enrolled in the study carried the G6PD WHO-class III mahidol variant, 487G>A.

The applicant concluded the hemolytic potential of TQ was dose-dependent and greater in those with lower G6PD enzyme activity levels and that the degree of hemolysis associated with a single 300 mg dose of TQ was similar to that with PQ 15 mg once daily for 14 days.

Figure 12.4
Maximum decline in haemoglobin up to Day 14 and baseline enzyme activity by G6PD status



Note: G6PD deficient subject 210 on TQ 200mg had maximum 23g/L decline in haemoglobin but met DLT criteria with haematocrit decline > 7.5%
pyr3043: /arenv/arprod/sb252263/taf110027/final/drivers/f_g6pdstathaemo_124.sas 14JUN2013 10:56

Source: Applicant's study report of TAF110027 (Pg. 307 /361)

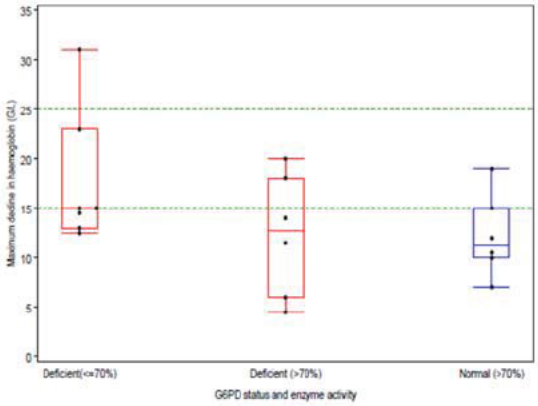
Of more relevance, the applicant reports weak association between enzyme activity and maximum decline in hemoglobin in the TQ 200mg cohort of G6PD-deficient subjects. This association is not confirmed by a statistical test due to the small sample size.

Table 8 **Summary of Maximum Decline in Haemoglobin up to Day 14 for Tafenoquine 200 mg Cohort (Safety Population)**

Subject	Age (y)	G6PD status	Mutation	G6PD Enzyme Activity (IU/gHb) (%)[a]	Maximum Hb Decline (g/L)	Day of Maximum Decline
Dose escalation scheme						
(b) (6)	24	Normal	-	12.3 (107)	-12.0	8
	22	Normal	-	12.9 (112)	-7.0	8
	28	Normal	-	11.8 (103)	-15.0	10
	25	Normal	-	11.4 (99)	-19.0	12
	19	Normal	-	13.6 (118)	-10.0	12
	22	Normal	-	10.9 (94)	-10.5	12
	23	Deficient	Mahidol	6.1 (53)	-31.0	10
	21	Deficient	Mahidol	6.6 (57)	-15.0	10
	25	Deficient	Mahidol	6.1 (53)	-15.0	9
	39	Deficient	Mahidol	6.3 (55)	-12.5	5
	39	Deficient	Mahidol	6.0 (52)	-13.0	14
	18	Deficient	Mahidol	6.3 (54)	-23.0	9
Subsequent cohort scheme (G6PD enzyme activity 61% to 80% site median normal value)						
(b) (6)	38	Deficient	Mahidol	8.6 (75)	-4.5	6
	19	Deficient	Mahidol	7.2 (62)	-14.5	8
Subsequent cohort scheme (G6PD enzyme activity 81%+ site median value)						
(b) (6)	19	Deficient	Mahidol	9.5 (83)	-18.0	9
	19	Deficient	Mahidol	10.0 (86)	-14.0	12
	42	Deficient	Mahidol	9.8 (85)	-6.0	8
	26	Deficient	Mahidol	9.8 (84)	-20.0	10
	30	Deficient	Mahidol	12.1 (105)	-11.5	7

Data Source: Listing 9.2, Listing 10.2
a. Enzyme activity percentage derived from site median of 11.54 IU/gHb
Hb haemoglobin

Figure 1.1
Maximum decline in haemoglobin up to Day 14 by G6PD status and enzyme activity in subjects dosed with TQ 200mg



Note: Enzyme activity as a percentage of site median 11.54 IU/gHB
lxd11930: /arenv/arprod/sb252263/taf110027/adhoc/drivers/adhoc1_boxplot_f101.sas 24JUN2013 10:49

Source: Applicant's study report of TAF110027 (Pg. 33 /361 and Pg. 317 /361)

In addition, the applicant reports that subjects with enzyme activity < 70% in the TQ 200 mg groups had similar median decline in hemoglobin to the subjects with > 70% enzyme activity, the range of decline was wider.

The applicant has proposed the warning that "Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing KRINTAFEL. (b) (4)

Reviewer's analysis

The applicant's evaluation of TAF110027 appears to be the source of the 70% threshold proposed in the warnings. This cut-off was applied to eligibility criteria in subsequent studies including the pivotal trials. Using the cut off proposed by the applicant, the median decline in hemoglobin for subjects deficient with <70% enzyme activity, deficient >70% activity, and Normal >70% activity is 15, 12.5 and 11.5 g/L respectively.

Applying the <60% cut-off widely cited in the literature to the data from subjects in the 200mg TQ cohort (Applicant's Table 8 in TAF11002 study report), the median maximum decline in hemoglobin for deficient subjects with <60% enzyme activity, deficient subjects with >60% activity and Normal subjects > 60% activity are 15, 14, and 11.5 g/L respectively. In this scenario, subjects who are G6PD-deficient with > 60% enzyme activity have a median maximum decline in hemoglobin closer to subjects who are G6PD-deficient with <60% activity. While it appears that the application of a 70% cut off is conservative, the difference between this scenario and the applicant's proposed cut-off lies with one subject. The applicant enrolled 2 subjects in the 60-80% deficient cohort, one of whom had enzyme activity > 70% and the other with enzyme activity < 70%. The sample size does not make a compelling case for assigning the 70% cut off.

The applicant proposed assessing hemolysis in moderate G6PD deficiency subjects defined as subjects with enzyme activity ≥40% <70% in a supportive study TAF116564. However, the applicant reported recruitment difficulty and discontinued enrollment.

Conclusion
While it is acknowledged that the phase 3 trials only included patients with >70% G6PD activity, there is no compelling evidence presented by the applicant to support a cut-off independent of a specific quantitative test. The inclusion of a cut-off value for enzyme activity, particularly one that deviates from prevalent definition, to define G6PD deficiency in the label may warrant considerations of G6PD assay performance and validation, which have not been addressed by the sponsor.

Recommendation
The (b) (4) enzyme activity cut-off proposed in the warning section of the proposed labeling should be removed and, where applicable, reference should be made to G6PD-deficient patients only.

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15.4.5.Review of Individual Study Reports

The following clinical pharmacology related individual studies were reviewed.

Study No.	Study information
1016RS	In vitro plasma protein binding in the rat, dog and man
1016V2	In vitro blood cell partitioning and the in vitro plasma protein binding in the rat, dog and man
2017N327858	In Vitro investigation of the transport of human p-glycoprotein, and of the passive membrane permeability of TQ
2014n213401	In Vitro Investigation of the role of CYP enzyme in the metabolism of TQ
RSD-101GZN	A comparison of the metabolism of TQ between preclinical species and man
2014N212406	In vitro evaluation of TQ as inhibitors for transporters
RSD-101HD5	In vitro evaluation of TQ as inhibitors of human CYP enzymes
2011 N114285	In vitro evaluation of TQ as inducer of human CYP3A4
SB252263/052	Pharmacokinetics, pharmacodynamics, safety and tolerance of a single oral dose of TQ
SB-252263/022	Food effect study of TQ
201780	Determination of the effects of dissolution profile on PK of single oral 300 mg doses of TQ tablets + 30 mg TQ stable isotope labelled (SIL) solution
TAF 110027	A Phase I study to investigate the hemolytic potential of TQ in healthy subjects with G6PD deficiency and compare to G6PD normal subjects
SB252263/015	An open-label study to determine the effect of TQ on the PK of desipramine in healthy volunteers
SB252263/040	Evaluation of the effect of TQ on the metabolism of multiple Cytochrome P-450 substrates
TAF106491	Drug-drug interaction study between TQ and CQ
200951	Drug-drug interaction study between TQ and artemisinin-based combination therapies (ACT)

Study No.: 1016RS

A preliminary investigation of the *in vitro* plasma protein binding of [14C]SB-252263 (TQ) in the rat, dog and man

Date(s): September 16, 1999 to January 26, 2000
Sponsor: Glaxosmithkline Intellectual Property Development LTD, England
Test facility: Drug Metabolism and Pharmacokinetics, Glaxosmithkline, England

METHODS
Pooled plasma was obtained from the male rat (Sprague-Dawley), dog (Beagle) and human (three healthy male volunteers). Total protein and albumin levels for each sample were determined prior to use to ensure they were within normal range. The *in vitro* plasma protein binding of [14C]SB-252263 was investigated in each species at target concentrations of 500 and 2000 ng free base/mL by equilibrium dialysis against isotonic PBS at approximately *37* °C over 5 hours. The radiochemical purities of both the stock solution used for spiking and the dialyzed plasma samples from each species were determined by radio-HPLC, to determine the stability of [14C]SB-252263 over the duration of the experiment and the error intervals of the protein binding.

Results
Reviewer Comment: While initial plasma concentrations were close to those targeted, the recovery of total radioactivity was approximately 80% at equilibrium. The investigator suggests this is likely due to non-specific binding to the dialysis cells and/or membranes and should not affect the quoted values for plasma protein binding at equilibrium.

The plasma and PBS concentrations of [14C]SB-252263 at equilibrium and the corresponding human *in vitro* plasma protein binding of [14C]SB-252263 is shown in

Table Table 1.

Table 1. In vitro plasma protein binding of [14C]SB-252263 in human plasma

Initial plasma conc. (ng fb/mL)	Equilibrium plasma conc. (dpm/g)	Mean equilibrium plasma conc. (dpm/g)	Equilibrium PBS conc. (dpm/g)	CF	% bound	Mean % bound
456	96829 98461	97645	593	1.41	99.57	99.50 +/- 0.06
	96387 98487	97437	69	1.33	99.46	
	96397 96259	96328	692	1.32	99.46	
1822	379096 377487	378292	1769	1.27	99.63	99.72 +/- 0.13
	392686	392199	1693	1.28	99.66	

Initial plasma conc. (ng fb/mL)	Equilibrium plasma conc. (dpm/g)	Mean equilibrium plasma conc. (dpm/g)	Equilibrium PBS conc. (dpm/g)	CF	% bound	Mean % bound
	391712					
	373850 373917	373883	622	1.33	99.88	

Volume shift correction factor (CF) = equilibrium plasma weight x (initial total weight/equilibrium total weight)
Source: NDA 210795

Reviewer Comment: In several samples, the equilibrium plasma concentrations were lower than the expected maximum plasma concentrations of SB-252263 noted in clinical and toxicology studies (400 and 3,000 ng/mL, respectively). The investigator was unable to determine the extent of plasma protein binding at concentrations significantly lower than those reporter (~370 ng/mL) due to limits on analytical sensitivity. The investigator proposes that the linearity of plasma protein binding from 370 to 1500 ng/mL can be extrapolated to these lower plasma concentrations.

The radiochemical purity of the compound in the stock spiking solution was found to be ~ 97%. Radio-HPLC of the dialyzed plasma samples showed that the radiochemical purity was reduced to ~ 87 and 82%, in rat and dog, respectively, suggesting some instability of the [14C]SB-252263 during the experiment. In dialyzed human plasma, the estimated radiochemical purity was ~ 94%, indicating little or no degradation over the 5 hour dialysis.

Reviewer Comment: Less than 0.5% of the total radioactivity (either SB-252263 or impurities/degradation products) were found to be unbound to plasma proteins. Therefore, the estimates of in vitro plasma protein binding are thought to be only marginally affected despite the low radio-chemical purities of the dialyzed plasmas.

Reviewer Assessment: The plasma protein binding of [14C]SB-252263 was very high (>99.5 %) with no evidence of difference between species.

Study No.: 1016V2

A preliminary investigation of the *in vitro* blood cell partitioning and the *in vitro* plasma protein binding of SB-252263 (TQ) in the rat, dog and man

Date(s): March 1, 1999 to March 25, 2009
Sponsor: Glaxosmithkline Intellectual Property Development LTD, England
Test facility: Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, England

METHODS

The *in vitro* blood: plasma partitioning of SB-252263 was determined in blood from each species at target concentrations of 100, 250 and 1000 ng free base/mL, after approximately 10 and 60 min mixing at ~37C. Blood was obtained from male rats (Sprague-Dawley), one male dog (Beagle) and one female human volunteer. The *in vitro* plasma protein binding of SB-252263 was investigated in each species at target concentrations of 250, 1000 and 5000 ng free base/mL by equilibrium dialysis against PBS (phosphate buffered saline) over 5 hours at ~ 37C. Pooled plasma was obtained from male rats (Sprague-Dawley), dog (Beagle) and three healthy male volunteers.

Concentrations of SB-252263 in blood, plasma and PBS were determined by LC/MS/MS following protein precipitation, as appropriate. The lower limit of quantification (LLQ) was 5 ng/mL and 1 ng/mL for a 50 uL aliquot of blood/plasma and PBS, respectively.

Results:
The *in vitro* blood cell association of SB-252263 in humans is detailed in Table 1.

Table 1. In vitro blood cell association of SB-252263 in humans

Target blood conc (ng fb/mL)	Time (min)	Mean [B] (ng fb/mL)	Mean [P] (ng fb/mL)	H	% BCA	[B]:[P] conc. Ratio
100	10 60	76.4 74.6	51.7 51.4	0.40 0.40	59 59	1.5 1.5
250	10 60	211.2 235.0	159.0 153.2	0.40 0.40	54 61	1.3 1.5
1000	10 60	879.8 843.3	619.6 653.1	0.40 0.40	58 54	1.4 1.3
			Mean +/- SD		57 ± 3	**1.4 ± 0.1**

[P] = measured concentration of SB-252263 in plasma
H = haematocrit, as determined by packed cell volume
% BCA = % association of SB-252263 with blood cells
The mean [B] and [P] results above represent the means of duplicate determinations
Source: NDA 210795

The plasma protein binding could not be accurately determined as the PBS concentrations were non-quantifiable at all 3 plasma concentrations.

REVIEWER ASSESSMENT: While a similar mean blood:plasma concentration ratio was noted in dog and man, it was significantly higher in rats. *In vitro* plasma protein binding could not be accurately determined in this study.

Study No.: 2017N327858

Title: An In Vitro Investigation of the Transport, via Heterologously Expressed Human P-glycoprotein, and of the Passive Membrane Permeability of SB-252263 (TQ) in MDCKII cells

Date(s): January 17, 2017 to May 1, 2017
Sponsor: Glaxosmithkline Intellectual Property Development LTD, England
Test facility: MSD ISDD GlaxoSmithKline King of Prussia, PA

METHODS
SB-252263 was evaluated as a substrate of the human P-glycoprotein (Pgp) transporter, and the passive membrane permeability was investigated, *in vitro*, using MDCKII-MDR1 cells transfected with the human MDR1 gene, which produces the Pgp protein. Amprenavir was selected as a positive control.

Results: The radiochemical purity of the stock solution of the positive control was 99% with no single impurity accounting for >1% of the detected radioactivity. Mass balance and efflux ratios are reported in Table 1. Table

Table 1. Transport and passive permeability in MDCKII-MDR1 Cells

Compound	Rate A→B (nmoles/h/cm²)	Rate B→A (nmoles/h/cm²)	Apical Efflux Ratio	A→B Mass Balance (%)	Corrected A→B Mass Balance (%)[1]	B→A Mass Balance (%)	Papp (nm/s) A>B + GF120918A	Papp (nm/s) B>A + GF120918A
20 μM SB-252263 (DMEM)	0.0018 ± NA	0.0043 ± 0.00055	ND	34 ± NA	110 ± NA	71 ± 3.9	-	-
20 μM SB-252263 (DMEM) + 5 μM GF120918A	0.0096 ± NA	0.0063 ± 0.00068	ND	38 ± NA	120 ± NA	73 ± 4.5	5.2 ± NA	1.8 ± 0.30
20 μM SB-252263 (DMEM + 4% BSA)	0.37 ± NA	0.056 ± 0.020	ND	25 ± NA	96 ± NA	79 ± 2.4	-	-
20 μM SB-252263 (DMEM + 4% BSA) + 5 μM GF120918A	0.12 ± 0.017	0.023 ± NA	ND	29 ± 4.0	120 ± 27	90 ± NA	98 ± 28	5.5 ± NA
20 μM SB-252263 (FaSSIF)	0.093 ± NA	0.69 ± 0.023	ND	41 ± NA	97 ± NA	86 ± 1.5	-	-
20 μM SB-252263 (FaSSIF) + 5 μM GF120918A	0.091 ± 0.0047	0.29 ± 0.078	ND	30 ± 6.2	90 ± 28	96 ± 2.6	69 ± 20	68 ± 19
3 μM [³H]amprenavir	0.033 ± 0.0074	0.52 ± 0.018	16	94 ± 1.1	-	94 ± 1.7	-	-
3 μM [³H]amprenavir + 5 μM GF120918A	0.20 ± 0.018	0.25 ± 0.004	1.2	97 ± 1.3	-	95 ± 3.6	-	-

Additional Information:
Data presented are the mean of 3 replicates unless otherwise noted. NA = not applicable (n=2)
ND=Not Determined due to compound association with cell monolayer/transwell membrane causing low mass balance..
1. Corrected Mass Balance determined by measuring the amount of SB-252263 associated with the cell monolayer and/or transwell membrane after the assay and adding it to the amount in the T_{90} receiver and T_{90} donor then dividing this sum by the amount in the T_0 donor then multiplying by 100.
Compounds were classified as Pgp substrates if apical efflux ratio >2. P_{app} values are the rate of the test compound in the A→B direction in the presence of GF120918. GF120918 was used in both the donor and receiver compartments @ 5 μM. Amprenavir was used as positive control.

Reviewer Comment: Mass balance for SB-252263 in the A to B direction was very low (25 to 41%). A corrected mass balance was then determined by measuring the amount of SB-252263 associated with the cell monolayer and/or transwell membrane after the assay and adding it to the amount in the T90 receiver and T90 donor, and dividing this sum by the amount in the T0 donor then multiplying by 100. The corrected value for mass balance in the A to B direction was 90 to 120%.

REVIEWER ASSESSMENT: Accurate efflux ratios could not be reliably determined due to SB-252263 associating with the cell monolayers /transwell membranes and/or getting trapped inside the cells, which resulted in altered drug transport rates in the test system.
Study No.: 2014n213401

An In Vitro Investigation into the Human Enzymology of SB-2522263 (TQ)

Date(s): September 23, 2013 – January 8, 2015
Sponsor: Glaxosmithkline Intellectual Property Development LTD, England
Test facility: Mechanistic Safety and Disposition, GlaxoSmithKline, England

OBJECTIVE(S):

- To investigate the human cytochrome P450 (CYP) enzymes responsible for the oxidative metabolism of SB-252263 by using appropriate *in vitro* test systems best suited to investigate low clearance compounds
- To investigate potential MAO enzymes responsible for the oxidative metabolism of SB-252263

METHODS

The oxidative metabolism of SB-252263 (5 and 10 uM) was investigated using a combination of *in vitro* systems: recombinant cytochrome P450 (rCYP) enzymes CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, recombinant monoamine oxidase enzymes (rMAO) rMAO-A and rMAO-B and pooled human hepatocytes using a 6-day 'relay' incubation method. Low clearance compounds (Timolol and Tolbutamide) were used as controls.

RESULTS

No additional metabolites were detected following incubation of SB-252263 with rCYP or rMAO enzymes. Negligible metabolism was observed over the 6-day relay period following incubations of SB-252263 with pooled human hepatocytes.

Reviewer Comment: The Sponsor notes that it was not possible to conclude whether the observed drug-related components in samples and controls, across the in vitro incubations investigated, were formed by metabolism and/or degradation. The Sponsor also cites high non-specific binding issues and questionable control results with the hepatocyte relay method that limit its utility as an in vitro tool.

REVIEWER ASSESSMENT: In this study, the Sponsor was unable to determine the enzymology responsible for oxidative hepatic metabolism of SB-252263.

Study No.: RSD-101GZN

A comparison of the metabolism of SB-252263 between preclinical species and man
Date(s): June 22, 1999 to October 23, 2000
Sponsor: Glaxosmithkline Intellectual Property Development LTD, England
Clinical Site: Glaxosmithkline Drug Metabolism and Pharmacokinetics, The Frythe, Welwyn, Herts, UK

OBJECTIVE(S):

- To investigate the metabolites of SB-252263 (TQ) in human urine and plasma
- To provide information on the likely routes of metabolism of SB-252263 in rat, dog and man using *in vitro* systems

METHODS

Human urine (predose and 48-72 h after the first dose) and plasma (predose, 60 and 84 h after the first dose) were obtained from clinical study 252263/014 where human volunteers received an oral dose of 400 mg free base of SB-252263-AX for each of three consecutive days, with food. HPLC-MS and HPLC with fluorescence detection were used to investigate possible metabolite structures in these samples.

[^{14}C] SB-252263-AX was incubated with human hepatocytes (10 uM) and rat, dog and human microsomes (10 uM or 1 mM).

RESULTS

At least 18 drug-related components were detected in human urine, resulting from O-demethylation, O-dearylation, deamination, N-dealkylation, oxidation, N-carbamylation, acetylation and glucuronide conjugation pathways. O-dearylation and O-demethylation were the two most common pathways. Drug-related material identified in human urine is consistent with the metabolites identified in rat and dog studies.
Unchanged SB-252263 was the only significant drug-related component detected in human plasma by HPLC-MS and HPLC with fluoresence detection.

Reported data is derived from a single experiment where [^{14}C] SB-252263-AX was incubated with human hepatocytes for 24 hours. Radioassay of a 24 hour cell extract indicated that 39% of the drug-related material was associated with the human hepatocytes. A further 61% was recovered in the medium making a total of 100% recovery of drug-related material in the cells plus medium. All radio- peaks detected in the hepatocyte medium by radio-HPLC were also detected in the no-cell control. Cell extracts at 24 hours contained only unchanged SB-252263.
No significant loss of drug-related material was observed following radioassay of all microsome incubations or extractions. Only unchanged SB-252263 was detected in rat, dog, human and denatured microsomes by radio-HPLC.

Reviewer comment: The Sponsor suggests that long term hepatocyte incubations are not ideal for studying the metabolism of SB-252263 due to the low rates of metabolism coupled with insolubility of SB- 252263 in the absence of BSA, cell death at 50 uM and instability of SB-252263 on extraction and in light.

REVIEWER ASSESSMENT: Drug-related material identified in human urine mainly resulted from O-dearylation and O-demethylation. Unchanged SB-252263 was the only significant component detected in human plasma. The cross-species metabolism or enzymology of SB-252263 could not be adequately determined in *in vitro* systems.

STUDY NO.: 2014N212406

In vitro evaluation of TQ as inhibitors for OCT2, MATE1 and MATE2-K

Date(s): 14 March 2014– 16 June 2014
Sponsor: GlaxoSmithKline R&D Ware, Hertfordshire, UK
Testing Site: (b) (4)

OBJECTIVES

To evaluate the ability of TQ to act as an inhibitor of the following transporters: organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporters 1 and 2-K (MATE1 and MATE2-K).

METHODS

Human embryonic kidney 293 (HEK293) cells expressing OCT2, MATE1 or MATE2-K (HEK293 cells transfected with a vector containing human OCT2, MATE1 or MATE2-K cDNA) and control cells (HEK293 cells transfected with vector only) were used. [^{14}C]Metformin was used as the Probe Substrate for OCT2, MATE1 and MATE2-K. Cimetidine was used as a positive control inhibitor for OCT2, MATE1 and MATE2-K. Quinidine was used as a positive control inhibitor for OCT2. Transporter expressing HEK293 cells and control cells were incubated with Hanks' Balanced Salt Solution (HBSS) solutions containing [^{14}C]metformin and TQ, cimetidine or quinidine. The adsorption of TQ was investigated on the assay plate with TQ concentration of 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 40 and 50 µM. Liquid chromatography tandem mass spectrometry (LC-MS/MS) was used to measure the concentration of TQ in the incubation solution. The mean observed concentration was treated as the actual concentration just after the incubation and was used for calculation of IC50 values. [^{14}C]Metformin radioactivity was measured by Liquid scintillation counter (LSC).

Calculation of Uptake Amount and Cleared Volume (OCT2, MATE1 and MATE2-K):

Uptake amount and cleared volume were calculated using the following equations:

[OCT2 and MATE1]:

$$\text{Uptake amount (dpm/well)} = \text{Radioactivity in cell lysate (dpm)} \times \frac{500\ (\mu L)}{300\ (\mu L)}$$

(conversion was made for the update amount in original 500 µL cell lysates when only 300 µL cell lysates was assayed)

[MATE2-K]:

$$\text{Uptake amount (dpm/well)} = \text{Radioactivity in cell lysate (dpm)} \times \frac{700\ (\mu L)}{500\ (\mu L)}$$

(conversion was made for the update amount in original 700 µL cell lysates when only 500 µL cell lysates was assayed)

Cleared volume (µL/mg protein)

$$= \frac{\text{Uptake amount (dpm/well)}}{\text{Protein amount (mg protein/well)} \times \text{Initial concentration (dpm/µL)}}$$

Calculation of Inhibitory Effects:

Inhibitory effects were calculated using the equation shown below from the cleared volume of expressing and control cells for test articles and positive control inhibitors:

$$\%\ \text{of control} = \frac{D - C}{B - A} \times 100$$

A: Cleared volume into control cells in the absence of TQ or a positive control inhibitor

B: Cleared volume into expressing cells in the absence of TQ or a positive control inhibitor

C: Cleared volume into control cells in the presence of TQ or a positive control inhibitor

D: Cleared volume into expressing cells in the presence of TQ or a positive control inhibitor

The percentage of control was rounded off to one decimal place.

Calculation of IC50 Value:

The IC50 value was calculated using the equation shown below from the relationship between percentage of control and test article or inhibitor concentration:

$$\%\ \text{of control} = C + \frac{D - C}{1 + (x/IC_{50})^b}$$

where

D: Upper limit of the percent of control

C: Lower limit of the percent of control or fixed as zero

x: Test article or inhibitor concentration

b: slope

The IC50 value was calculated using Phoenix WinNonlin 6.1 (Certara). The IC50 value was expressed to three significant figures and represented as the mean ± SE.

Calculation of Adsorption Ratio

The adsorption ratio was calculated from the following equation using Microsoft Office Excel 2003 (Microsoft) and rounded off to one decimal place.

$$\text{Adsorption ratio (\%)} = 100 - \frac{\text{Concentration after incubation (nM)}}{\text{Concentration before incubation (nM)}} \times 100$$

RESULTS AND CONCLUSIONS

The active uptake of [^{14}C]metformin (as a substrate in OCT2, MATE1 and MATE2-K transfected cells) was clearly observed, and the positive control inhibitors for each transporter were found to inhibit the transporter activities as expected in each assay.

The inhibitory effects and IC_{50} of TQ and positive inhibitors on OCT2, MATE1 and MATE2-K are summarized in Table 1.

Table 1: Summary of results: Inhibitory effects of TQ and probe inhibitors on human transporters

Isoform	Substrate	Test article or typical inhibitor	IC_{50} (μM) [a]	Percent of control at highest concentration (%)
OCT2	Metformin	SB-252263	0.282 ± 0.064	3.4
		Cimetidine	43.2 ± 11.6	4.9
MATE1	Metformin	SB-252263	1.99 ± 0.30	6.2
		Cimetidine	0.508 ± 0.044	5.4
MATE2-K	Metformin	SB-252263	0.632 ± 0.279	5.8
		Cimetidine	8.86 ± 1.61	3.0

a: Average data obtained from triplicate samples for each test article or typical inhibitor concentration were used to calculate IC_{50} values. Each value represents the mean ± SE.

SB-252263: TQ

The adsorption ratio of TQ to the assay plate was determined. After incubation in HBSS (pH 7.4 or pH 8.5) for 2 or 5 min, the adsorption ratios were 35.9% to 78.7% or 39.7% to 85.2%, respectively. In consideration of the actual concentration of TQ during the incubation, the Table 1 reported IC_{50} values could be 4-7 lower and were calculated to be 0.0419 ± 0.0126 μM for OCT2, 0.435 ± 0.024 μM for MATE1, and 0.170 ± 0.073 μM for MATE2-K.

REVIEWER'S ASSESSMENT

Study 2014N212406 determined the inhibitory effects and IC50 of TQ and positive inhibitors on human transporters of OCT2, MATE1 and MATE2-K. Based on the median level of unbound plasma Cmax of TQ (approximately 0.007 μM) following single oral dose of TQ 300 mg, the

estimated Cmax,u/IC_{50} ratio are lower than FDA recommended cutoff values (0.1 for OCT2, 0.02 for MATEs) indicating low in vivo potential of the inhibitory effect. Even using the lower IC_{50} values after taking into account the non-specific binding of TQ to the assay plate, the estimated Cmax,u/IC_{50} ratios are either very close to the cutoff value for OCT2 or slightly higher than the cutoff value for MATEs. Given the single dose regimen and high protein binding of TQ, the review team considers that the risk for TQ to inhibit human OCT2 and MATE transporters is low.

STUDY NO.: RSD-101HD5

An In Vitro Evaluation of the Inhibitory Potential of TQ on Human Cytochrome P450 Enzymes

Date(s): 15 September 1999– 12 December 2000
Sponsor: GlaxoSmithKline R&D Ware, Hertfordshire, UK
Testing Site: (b) (4)
Analytical Site:

OBJECTIVES

To determine the potential of TQ to inhibit the major cytochrome P450 enzymes (CYP) (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A9/11) in human liver microsomes.

METHODS

TQ was supplied as the hydrogen succinate salt. Enzyme activities, presented in Table 1, were measured, using probe substrates, in the presence and absence of TQ..

Human liver microsomes (HLM) was used in this study. The pooled HLM sample was prepared from nine individual samples. This pooled sample was used in the determination of the Ki values and as the "medium-activity" HLM sample for all the metabolism-dependent experiments. In designing the various experiments, the kinetic constants, Km and Vmax, determined for a different pooled HLM sample (prepared from seven individuals) were used to select the probe substrate concentrations and incubation conditions.

In Part 1, the ability of TQ to directly and reversibly (metabolism-independent) inhibit the major cytochrome P450 enzymes in a pooled human liver microsomal sample was evaluated and the corresponding inhibitory constants (Ki values) were calculated.

In Part 2, the ability of TQ to act as a reversible metabolism-dependent inhibitor and as an irreversible or quasi-irreversible metabolism-dependent inhibitor of the CYP450 enzymes listed was investigated using two individual HLM samples and the pooled HLM sample.

Table 1 lists the human CYP450 enzyme activities, using probe substrates, that were evaluated in the assessment of the metabolism-independent and metabolism-dependent inhibitory potentials of TQ.

Table 1. Measurement of human CYP450 enzyme activities by using probe substrates

Cytochrome P450 Enzyme	Activity Measured
CYP1A2	7-Ethoxyresorufin *O*-dealkylation
CYP2A6	Coumarin 7-hydroxylation
CYP2C8	Paclitaxel 6α-hydroxylation
CYP2C9	Diclofenac 4′ –hydroxylation
CYP2C19	*S*-Mephenytoin 4′ –hydroxylation
CYP2D6	Dextromethorphan *O*-demethylation
CYP2E1	Chlorzoxazone 6-hydroxylation
CYP3A4/5	Testosterone 6β-hydroxylation
CYP3A4/5	Midazolam 1′-hydroxylation
CYP3A4/5	Nifedipine oxidation
CYP4A9/11	Lauric acid 12-hydroxylation

RESULTS AND CONCLUSIONS

Table 2 lists the Ki values determined for CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 (three different probe substrates evaluated), and CYP4A9/11 using the pooled HLM sample.

Table 2. In vitro inhibition of cytochrome P450 enzyme activities in human liver microsomes by TQ

Cytochrome P450 enzyme	Activity measured	Metabolism-independent				Metabolism-dependent[c]
			IC50 (uM)			
		Ki[a] (uM)	Individual[b]	Mean	Type of inhibition	Reversible/Irreversible
CYP1A2	7-Ethoxyresorufin *O*-dealkylase	5.2	12, 18, 18	16	mixed	no effect observed
CYP2A6	Coumarin 7-hydroxylase	7.1	6.9, 6.6, 6.5	6.7	noncompetitive	no effect observed
CYP2C8	Paclitaxel 6α-hydroxylase	8.8	6.0, 6.3, 9.3	7.2	noncompetitive	no effect observed
CYP2C9	Diclofenac 4′-hydroxylase	1.8	5.5, 4.5, 4.5	4.8	mixed	no effect observed
CYP2C19	*S*-Mephenytoin 4′-hydroxylase	54	Not determined[d]	-	competitive	no effect observed
CYP2D6	Dextromethorphan *O*-demethylase	15	20, 21, 20	20	noncompetitive	no effect observed
CYP2E1	Chlorzoxazone 6-hydroxylase	81	Not determined[d]	-	noncompetitive	no effect observed
CYP3A4/5	Testosterone 6β-hydroxylase	1.6	2.9, 3.3, 4.1	3.4	competitive	no effect observed
CYP3A4/5	Midazolam 1′-hydroxylase	7.2	8.4, 8.5, 8.8	8.6	noncompetitive	no effect observed
CYP3A4/5	Nifedipine oxidase	10	7.6, 8.1, 10	8.6	noncompetitive	no effect observed
CYP4A9/11	Lauric acid 12-hydroxylase	18	27, 28, 27	27	noncompetitive	no effect observed

Note: Values were calculated using the average data obtained from duplicates for each incubation condition. The Ki and IC50 values were calculated using GraFit software with simple weighting.
a: Determined using the pooled microsomal sample.
b: Values obtained from microsomal samples with low, medium and high activity, respectively, for the selected enzyme
c: Evaluated using the pooled microsomal sample and two individual microsomal samples.
d: Not determined since inhibition was weak.

The in vitro incubation of TQ with human liver microsomal (HLM) preparations in the presence of specific probe substrates demonstrated that SB- 252263 has the potential to inhibit several human cytochrome P450 enzymes.

- In human liver microsomes, TQ was a significant inhibitor of CYP1A2, CYP2A6, CYP2C8, CYP2C9, and CYP3A4/5. For CYP3A4/5, the degree of inhibition varied with the probe substrate used. The most pronounced inhibition was on the activities of diclofenac 4¢-hydroxylase (Ki 1.8 uM) and testosterone 6b-hydroxylase (Ki 1.6 uM).

- TQ was a moderate inhibitor of CYP2D6 and CYP4A9/11, and a weak inhibitor of CYP2C19 and CYP2E1.
- There was no evidence for metabolism-dependent inhibition of the evaluated CYP450 enzymes.

REVIEWER'S ASSESSMENT

Study RSD-101HD5 determine the inhibitory effects and Ki values of TQ on the major cytochrome P450 enzymes (CYP) (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A9/11) in human liver microsomes. One drawback of the study design is a lack of appropriate strong inhibitors as positive controls, which is recommended by the following FDA guidance: In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies (October 2017). However, the potential of TQ to inhibit the CYP enzymes was further evaluated in clinical studies. In general, we concur with the Applicant's results from this study.

STUDY NO.: 2011 N114285

Activation of Human PXR by TQ, SB-252263-AX

Date(s): 21 February 2011– 29 March 2011
Sponsor: GlaxoSmithKline R&D Ware, Hertfordshire, UK
Testing Site: GlaxoSmithKline Medicines Research Centre, Herts, SG1 2NY, UK
Analytical Site: GlaxoSmithKline Medicines Research Centre, Herts, SG1 2NY, UK

OBJECTIVES

To examine the ability of TQ, SB-252263-AX to activate the human Pregnane-X-Receptor (PXR).

METHODS

The human hepatoma cell line (HEPG2) is used as a host cell. These cells are transfected with full length human PXR and a reporter gene construct containing the upstream regulatory sequence of CYP3A4 (containing the binding sites for PXR) linked to a luciferase reporter gene.Activation of human PXR by a compound is expressed as a percentage of that achieved with rifampicin (10 μM) positive control. When a full dose response curve is achieved, the pEC50 value can be calculated. If a full dose response curve is not achieved, the pEC50 value is reported as "< -logmax concentration tested".

Interpretation of Results:

% Max	pEC_{50}	Interpretation
0%	<	No response
<30%		Weak response
30 -70%		Moderate response
>70%	<	PXR activation at high concentrations only
>70%	value	PXR activation with some potency

RESULTS AND CONCLUSIONS

Table 1 shows the activity of TQ against hPXR. TQ was much less potent than the standard agonist, rifampicin, when run at the same time.

Within the 0.001-50µM concentration range of this investigation, TQ failed to trigger a response, and only on one occasion out of 11 did the maximum response reach 30% of that achieved with rifampicin (10 µM), the positive control. Therefore, the quoted pEC50 is <4.3. However, it was observed that at the two highest concentrations (50µM and 16.6µM), TQ had an apparent toxic effect upon the cells.

Table 1. Activity of TQ against hPXR

Compound	pEC50 (Mean) ± StdDev	N	Max Response (% Mean) ± StdDev	N
SB-252263-AX	<4.3	7	16.5 ± 9.3	11*
SKF-39973	6.2 ± 0.2	21	111.2 ± 22	21

*SB-252263-AX was tested 11 times. On one occasion, it failed to fit a curve but the max response was reported, on 10 occasions data was reported with a modifier. On 7 occasions out of 11, data was reported as <4.3, on 3 occasions data was reported as <5.26 (as the last two points were excluded due to toxicity of the compounds at high concentration).

SB-255563-AX=TQ; SKF-39973=Rifampicin

REVIEWER'S ASSESSMENT

We concur with the conclusion from this study that TQ did not induce CYP3A4 in PXR transfected hepatocytes.

STUDY NO.: SB252263/052

Pharmacokinetics, Pharmacodynamics, Safety and Tolerance of a Single Oral Dose of WR 238605 Succinate

Date(s): September 1993 – December 1993
Sponsor: Glaxosmithkline Intellectual Property Development LTD, England
Clinical Site: Walter Reed Anny Medical Center, Walter Reed Army Institute of Research, Fort Detrick, MD

Analytical Site: (b) (4)

METHODS

Study SB252263/052 was an open-label study to assess the pharmacokinetics, pharmacodynamics, safety and tolerance of WR 238605 Succinate in healthy adult male volunteers. Subjects were randomly divided into 3 phases corresponding to the three ascending dose levels (100, 200 and 400 mg base). Subjects fasted after midnight and received the drug at about 0800 on day 0 with 6-8 ounces of water.

The capsule(s) of WR 238605 (TQ) succinate used in the study was manufactured by the (b) (4)

PK Sample Collection**:** Twenty blood and plasma samples were obtained up to 44 days in all subjects.

Analytical Methods: Pharmacokinetic samples were analyzed for WR 238605 succinate by validated HPLC. This assay had a sensitivity of 1 ng/ml for plasma and 2 ng/ml for blood, with both intra- and inter-day coefficients of variation of <10%.

RESULTS

Pharmacokinetic analysis was performed on the plasma drug concentrations using non-compartmental (Table 1) and compartmental (Table 2

Table) methods, in which concentration data were analyzed using a one-compartment model with first order absorption and elimination. Both demonstrated linear kinetics at the doses studied, with a t_{max} of 12 hours, an elimination half-life of two weeks, and a large volume of distribution suggested of extensive tissue distribution. Blood and calculated RBC concentrations were 2.0 and 3.4 times higher than corresponding plasma concentrations.

Table 1. Noncompartmental Parameter Estimates of WR 238605 (Mean ± SD)

	T_{max} (hr)	AUC_{total}	Cmax	$T_{1/2}$ (hr)	CL (L/hr)	Vss/f (L)	Absorption time	Residence Time
100 mg	20.1 ± 6.1	18.02 ± 2.61	46.7± 12.6	336 ± 40	5.65 ± 0.86	2729 ± 654	5.0 ± 1.5	480 ± 58
200 mg	19.2 ± 17.2	39.55 ± 4.25	96.5 ± 12.2	340 ± 70	5.11 ± 0.57	2445 ± 465	5.7 ± 1.6	482 ± 90
400 mg	21.8 ± 17.2	82.76 ± 17.51	183.8 ± 29.9	363 ± 44	5.01 ± 1.04	2557 ± 421	5.9 ± 2.5	516 ± 61
Mean±SD	20.4±13.6	N/R	N/R	346 ± 51	5.26 ± 0.85	2577±506	5.5±1.9	492±69

N/R: not reported

Reviewer Comment: While the mean T_{max} was 20.4±13.6 hours, the median value was 12.3 hours. This median value is similar to what was reported in a previous ascending dose study. The investigator states that this difference was due to a few individuals whose T_{max} occurred late (24-50 hours), and likely reflects assay or biological variability.

Table 2. Population Pharmacokinetic Parameters of WR 238605

	Cl/f (L/h)	V/f (L/kg)	Ka (hr^{-1})	Tlag (h)
Estimate	5.32	34.8	0.31	0.46
SEE	0.23	0.96	0.03	0.02
SEE as % CV	4.30	2.77	10.71	4.11
Inter-individual Variability (%)	14.6	10.9	45.3	7.6

SEE =Standard Error of the Estimate
Source: NDA 210795

Reviewer Comment: In this study, WR 328605 was best described by a one-compartment model. In some individuals, peak concentrations were under-predicted; however, a 2-compartment model did not significantly improve the fits. The Sponsor recognizes the limitations of obtaining population PK parameters from a small homozygous cohort of eighteen healthy male subjects.

REVIEWER ASSESSMENT: TQ appeared to have dose proportional kinetics and a half-life of approximately 2 weeks.

STUDY NO.: SB-252263/022

An open label, single dose, two parallel group study to investigate the effect of food on the bioavailability of the TQ final capsule formulation, in healthy male and female volunteers

Date(s): January 2001 – April 2001
Sponsor: Glaxosmithkline Intellectual Property Development LTD, England
Clinical Site: FOCUS Clinical Drug Development GmbH, Neuss, Germany
Analytical Site: (b) (4)

METHODS
This study was an open label, randomized, single dose, parallel-group design, to assess the effect of food on SB-252263 (TQ) pharmacokinetics in healthy male and female volunteers.

Two regimens were studied:

A. One capsule of SB-252263 200 mg taken orally in the fasted state (fasted group)

B. One capsule of SB-252263 200 mg taken orally immediately (within 5 minutes) after completion of a standard FDA high-fat meal (2 strips of grilled bacon, 2 eggs cooked in butter, 2 slices of toast, 2 pats butter, 4 oz hash brown potatoes, 300 mL whole milk) which had to be consumed within 30 minutes (fed group)

Subjects consumed 240mL of water at two and four hours after dosing. Lunch was given approximately five hours after dosing, and dinner approximately 10 hours after dosing. One evening light snack was permitted between 12 hours and 16 hours post-dose.

TQ was supplied as size 1, hard gelatin capsules each containing TQ 200 mg (pure free base).

PK Sample Collection: Plasma concentrations were collected pre-dose, up to 24 hours (n=11 samples), at 3, 4, 5, 7 days post dose and weekly (+/- 1 day) for 8 weeks post dosing.

Analytical Methods:
Plasma samples were analyzed using a protein precipitation extraction procedure with methanol followed by a validated LC/MS/MS method. The assay demonstrated acceptable performance in human plasma in a three-run validation over a concentration range of 5 ng/mL to 500 ng/mL, with R^2 values $\geq$ 0.998. Bias and precision were also satisfactory, with all reported values < 8 %.

RESULTS
Study Population: In total, 40 healthy subject (20 female and 20 male subjects) were recruited.

Pharmacokinetics
Pharmacokinetic parameters following 200 mg single TQ dose administration to healthy male and female volunteers in the fasted and fed states were presented in Table 1. The point estimates and 90% confidence intervals for the comparisons between fed and fasted administration are listed in Table 2**.**

Table 1. Mean (SD) Pharmacokinetic Parameters Following 200 mg Single TQ Dose Administration to Healthy Male and Female Volunteers in the Fasted and Fed States

Parameter	Fasted (n=20)		Fed (n=20)	
	Value (mean, SD)	CV%	Value (mean, SD)	CV%
AUC(0-inf) ug.h/mL	51.1 (22)	49.8	69.7 (24.4)	31.3
Cmax, ng/mL	122 (43)	47.2	166 (84)	43
Tmax*, h	13 (6-72)	NA	14 (5.62-144)	NA
T1/2, days	15.4 (2.6)	NA	15.5 (11.6)	NA

*Data presented as median (range); NA: Not available; Source: NDA 210795

Table 2. Point Estimate and 90% Confidence Intervals for TQ AUC(0-inf) and Cmax for the Fed Regimen Relative to the Fasted Regimen

Parameter	Comparison	Ratio	90% C.I.	CVresid
AUC(0-inf)	Fed:fasted	1.41	1.15, 1.72	38.8
Cmax	Fed:fasted	1.31	1.07, 1.62	40.8

Source: NDA 210795

REVIEWER ASSESSMENT: When TQ was administered at 200 mg as capsule with a high fat meal, TQ plasma AUC and C_{max} increased on average by 41% and 31%, respectively, as compared to the fasted state. Similar food effect is expected for the to-be-marketed tablet formulation.

STUDY NO.: 201780

A randomized, open-label, single-period, parallel-group study in healthy subjects to determine the effects of dissolution profile on the pharmacokinetics (via both venous and peripheral microsamples) of single oral 300 mg doses of TQ (SB- 252263) tablets + 30 mg TQ stable isotope labelled (SIL) solution

Date(s): May 18, 2016 – August 3-, 2016
Sponsor: Glaxosmithkline Intellectual Property Development LTD, England
Clinical Site: PAREXEL Early Phase Clinical Unit, Baltimore Harbor Hospital Center, Baltimore, MD
Analytical Site: (b) (4)

OBJECTIVE(S):

- Primary: To determine the relative bioavailability of TQ (TQ) from tablets exhibiting different dissolution profiles in healthy subjects

METHODS

This was a single-center, 2-arm, randomized open-label, parallel-group study in healthy volunteer subjects. Randomization was stratified by baseline weight (<80 kg, ≥80 kg) and subjects were randomized in the ratio 1:1 within each arm.

- Arm 1: Arm 1: TQ 300 mg control product + 30 mg TQ SIL in oral solution
- Arm 2: Arm 2: TQ 300 mg Dissolution profile X ('Intermediate aged' TQ product) + 30 mg TQ SIL in oral solution

TQ was dosed in the fed state to healthy adult male subjects.

Table 1. Summary of Investigational Products

	Study Treatment		
Product name:	Tafenoquine (SB-252263)	Tafenoquine (SB-252263)	Tafenoquine (SB-252263)
DP Product Code (Unique Identifier)	Control Product[1]	Dissolution Profile X[2]	SIL product
Batch numbers	Input batch # 152391457	Input batch # 152393154	Batch # GB105959-028A1
Formulation description:	Each tablet contained 150 mg tafenoquine	Each tablet contained 150 mg tafenoquine	0.25 mg/mL aqueous Solution of SIL Tafenoquine (SB252263)
Dosage form:	Film-coated tablet	Film-coated tablet	Aqueous solution
Unit dose strength(s)/ Dosage level(s):	150 mg	150 mg	0.25 mg/mL (120 mL to be dosed, equivalent to 30 mg)
Route of Administration	Administered 2 tablets orally	Administered 2 tablets orally	Oral
Dosing instructions:	Administered with water after a meal	Administered with water after a meal	Administer with water after a meal
Physical description:	A dark pink, capsule-shaped, film-coated tablet that was plain on both sides.	A dark pink, capsule-shaped, film-coated tablet that was plain on both sides.	Clear solution
Manufacturer:	GlaxoSmithKline	GlaxoSmithKline	Compounded at site

1. TQ 300 mg Control
2. TQ 300 mg Intermediate Aged
Source: NDA 210795

Reviewer Comment: The original study contained 3 arms (intermediate aged, aged, and SIL tablets), but was modified to the current design when the study team determined the aged tablets were not of sufficient quality for human dosing. This is acceptable given the negative study results (i.e., no difference between control and intermediate aged tablets).

PK Sample Collection: Plasma samples were obtained pre dose and up to 56 days post dose.

Analytical Methods: Plasma samples were analyzed for SB-252263 and SB-252263 M+5 (SIL) using a validated analytical method based on protein precipitation, followed by LC-MS-MS analysis. The lower limit of quantification (LLQ) for SB252263 and SB252263 M+5 was 0.5 ng/mL using a 7 µL aliquot of human plasma with a higher limit of quantification (HLQ) of 500 ng/mL. Results were satisfactory at all validation sample concentrations examined with accuracy between 85% and 115% (80-120% at the LLQ) and within- and between-run precision values within 15% (20% at the LLQ).

RESULTS

Pharmacokinetics: Exposure data from peripheral sampling were comparable to the venous sampling PK data except at the higher concentration range.

Table 2. Summary of Treatment Comparison of TQ (Venous Sample) Pharmacokinetic Parameters following administration of 300 mg TQ tablets + 30 mg TQ SIL in solution

PK Parameter	TQ 300 mg Intermediate Aged		TQ 300 mg Control		Ratio (TQ 300 mg Intermediate Aged/ TQ 300 mg Control)		CVb (%)
	n	Geometric LS Mean	n	Geometric LS Mean	Estimate	90%CI	
AUC(0-∞) (h*ng/mL)	7	100,072	7	97,109	1.03	(0.98, 1.08)	5.20
AUC(0-∞)* (h*ng/mL)	7	97,658	5	95,551	1.02	(0.96, 1.09)	5.58
AUC(0-t) (h*ng/mL)	7	91,292	7	88,536	1.03	(0.98, 1.09)	5.24
C_{max} (ng/mL)	7	225.5	7	224	1.01	(0.95, 1.07)	5.48

Source: NDA 210795

Reviewer Comment: Microsampling data comprise a secondary objective and was used as an exploratory endpoint to help design future studies.

REVIEWER ASSESSMENT: Differences in the observed *in vitro* dissolution profiles of the intermediate aged batch and control batch did not result in any clinically relevant differences in systemic TQ exposure. The original study design was modified from 3 arms to 2, excluding an 'aged tablet' group.

STUDY NO.: TAF 110027

A Phase I Study to Investigate the Hemolytic Potential of TQ in Healthy Subjects with Glucose-6-Phosphate Dehydrogenase Deficiency and the Safety and Tolerability of TQ in Acute *Plasmodium vivax* Malaria Patients with Glucose-6-Phosphate Dehydrogenase Deficiency

Date(s): 02 July 2009– 01 April 2013
Sponsor: GlaxoSmithKline (GSK) R&D Ware, Hertfordshire, UK
Testing Site: (b) (4)

Analytical Site

OBJECTIVES

The primary objective was to evaluate the safety, tolerability and hemolytic potential of TQ (TQ) in heterozygous glucose-6-phosphate dehydrogenase (G6PD)-deficient (World Health Organization [WHO] class III variant) female healthy volunteers compared with G6PD-normal female healthy volunteers.

Secondary objectives were to evaluate changes in other clinical laboratory markers for hemolysis (such as haptoglobin, reticulocytes and bilirubin levels), to characterize the pharmacokinetics of TQ in G6PD-deficient healthy volunteers, and to explore the potential pharmacokinetic (PK)/pharmacodynamic (PD) relationships of TQ in G6PD-normal and G6PD-deficient healthy volunteers.

METHODS

Trial Design

This was an open-label, single dose, dose-escalation study using a stepwise risk exposure approach. The hemolytic potential of TQ was assessed in G6PD-deficient heterozygous (WHO Class III variant) female healthy volunteers. G6PD-normal female healthy volunteers were enrolled as the control with both groups receiving TQ (i.e., no placebo was used). The study also assessed the hemolytic potential of PQ (PQ) 15 mg OD x14 days when given to G6PD-deficient healthy subjects as a control arm.

For the dose escalation phase, G6PD-deficient heterozygous female healthy volunteers with enzyme activity range 40% to 60% of the site median normal value were recruited. Proposed total TQ doses of 100 mg, 200 mg, 300 mg, 400 mg, and 600 mg TQ single dose taken with food were planned to determine the hemolytic potential of TQ and characterize the dose-response relationship. Once the highest non-hemolytic dose (HND) had been defined, additional cohorts exploring the hemolytic potential of TQ in G6PD-deficient heterozygous females with 61% to 80% and 81+% enzyme activity of the site median normal value were planned to be recruited in parallel.

The dose escalation scheme and numbers of G6PD-deficient heterozygous and G6PD-normal female healthy volunteers that were planned to be recruited are detailed in **Table 1**.

Table 1 Dose Escalation Scheme

Cohort	Daily Dose x days	G6PD-deficient Subjects (n)[b]	G6PD-normal Subjects (n)[c]
TQ[a]			
A1	100mg x1	6	6
A2	200mg x1	6	6
A3	300mg x1	6	6
A4	400mg x1	6	6
A5	600mg x1	6	6

a. Dose escalation continued until the HND was reached. HND was defined as having ≤2 of 6 subjects experiencing dose-limiting toxicity.
b. These cohorts had G6PD-deficient subjects with enzyme activity 40% to 60% of the site median normal value.
c. These cohorts had G6PD-normal subjects with >80% enzyme activity of the site median normal value.

Both TQ and PQ were taken with food in this study

At each dose level, if no dose-limiting toxicity (DLT) was observed during the initial 14-day period, enrolment began for the next higher dose level following a dose escalation/safety

review meeting. Dose escalation was to be continued until the required numbers of DLTs were observed or the maximum dose level of 600 mg was reached in the absence of sufficient DLTs.

Once the HND had been defined, additional cohorts exploring the hemolytic potential of TQ in G6PD-deficient heterozygous females with 61% to 80% and 81%+ enzyme activity of the site median normal value were recruited in parallel. Subject numbers for these cohorts are detailed in **Table 2**. The PQ arm was added as a positive control to assess the effects of a known hemolytic agent in the study population.

Table 2 Subsequent Cohort Scheme

Cohort	Daily Dose x days	G6PD-deficient subjects (n)	G6PD Enzyme Activity[a]	G6PD-normal Subjects (n)	G6PD Enyme Activity[a]
TQ					
A6[b]	HND x1	6[c]	61% to 80%	0	N/A
A7[b]	HND x1	6[c]	81%+	0	N/A
PQ					
A8	15mg x14	6	40% to 60%	6	>80%

a. G6PD enzyme activity of site median normal value.
b. These cohorts were recruited in parallel, with a maximum of three subjects dosed from each cohort at one time.
c. Up to six G6PD-deficient subjects were recruited.

Assessments

Hematologic Stopping Criteria

DLT criteria for hematologic stopping were defined as subject(s) experiencing a ≥2.5 g/dL decline in Hb (or ≥7.5% decline in Hct) from baseline or displaying clinically significant signs and symptoms of hemolysis (e.g., pallor, hemoglobinuria, jaundice, acute renal failure, tachycardia, tachypnea, hypotension etc.).

Pharmacokinetic Assessments

Ten plasma samples per subject were collected for PK assessments at Days 1, 2, 3, 4, 5, 7, 14, 21, 28, 56 following drug administration.

From the single dose TQ and PQ Day 1 plasma concentration-time data, the following PK parameters were determined, as data permitted: Cmax, Tmax, AUC from time zero to the last quantifiable time point (AUC[0-t]) and AUC from time zero to infinity (AUC[0-∞]).

Pharmacodynamic Assessments

Six blood samples per subject were collected for PD assessments at Days 1, 2, 3, 4, 5, 7 following drug administration.

Exploratory graphical assessments were undertaken to examine the relationships of TQ and PQ concentrations with the change from baseline Hb levels over time. Also, TQ and PQ PK

parameters (e.g., AUC, Cmax) by dose groups were compared to the maximum change from baseline Hb levels.

Analytical Methods:

Plasma samples were analyzed for TQ or for PQ by using validated analytical methods based on protein precipitation, followed by HPLC tandem mass spectrometry (HPLC/MS/MS) analysis. The lower limit of quantification (LLQ) for TQ was 2 ng/mL and a higher limit of quantification (HLQ) of 3000 ng/mL using a 50 µL aliquot of EDTA plasma. The LLQ for PQ was 2 ng/mL using a 50 µL aliquot of human plasma with a HLQ of 500 ng/mL.

The PD assessments were conducted using the standard laboratory measurements of Hb and Hct.

Reviewer's Comments: The performance of the bioanalytical methods for plasma TQ and PQ has been evaluated by the Applicant. The bioanalytical methods are acceptable.

RESULTS AND CONCLUSIONS

A total of 51 healthy females (with moderate G6PD deficiency + normal controls) who received TQ 100 mg, 200 mg and 300 mg or PQ 15 mg OD x 14 days completed the study. Only 7 of the intended 12 subjects had been recruited to the two subsequent cohorts (planned each of n=6) for TQ in patients with 61% to 80% and 80%+ enzyme activity. According to the Applicant, the decision was made to end the study early following a detailed review of total study data generated from which it was concluded that sufficient information on the toxicity of TQ in G6PD-deficient subjects with enzyme levels >60% had been obtained from those 7 subjects with G6PD enzyme activity >60% that have been recruited.

Pharmacokinetic Results

TQ PK results are presented in **Table 3**. PK parameters of PQ were determined by the Applicant and results are not included in this review.

Table 3: Summary of Selected Plasma TQ Pharmacokinetic Parameters[a]

Treatment	G6PD Status	N	AUC (0-∞) (ng.h/mL)	AUC (0-t) (ng.h/mL)	Cmax (ng/mL)	tmax (h)[b]	$t_{1/2}$ (h)
Tafenoquine 100 mg	Normal	6	27062 (8.00)	25259 (8.00)	71.9 (12.0)	27.0 (8.00-48.0)	336 (16.0)
	Deficient	6	31466 (21.0)	29875 (19.0)	87.6 (21.0)	21.0 (12.0-48.0)	292 (24.0)
Tafenoquine 200 mg	Normal	6	81768 (15.0)	76570 (12.0)	223 (14.0)	24.1 (8.00-48.0)	328 (19.0)
	Deficient	13	81146 (25.0)	74887 (25.0)	204 (29.0)	24.1 (8.00-48.0)	353 (20.0)
Tafenoquine 300 mg	Normal	6	145857 (22.0)	133041 (20.0)	350 (16.0)	12.1 (12.0-36.0)	374 (17.0)
	Deficient	3	110458 (43.0)	105860 (41.0)	467 (37.0)	12.0 (2.00-48.0)	295 (24.0)

a. Geometric Mean (CVb%)
b. Median (range)

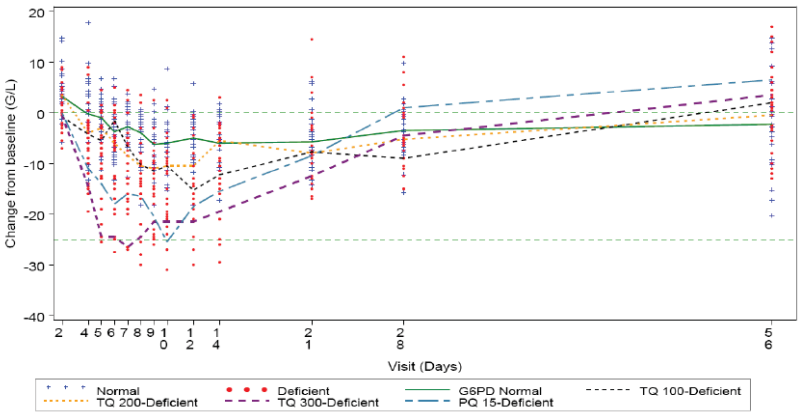
Reviewer's Comments: Cmax and AUC values for the 200 mg dose in this study were higher than those observed in a food effect study using 200 mg TQ under fed conditions (SB252263/022).

Cmax values at the 300 mg dose in the current study were somewhat higher than those in the TQT study, TAF114582. The reason for the higher Cmax and AUC values observed in this study is unclear. Of note, the TQ drug exposures (Cmax and AUC) were increased in a greater than dose proportional manner in this study.

Pharmacodynamic Results

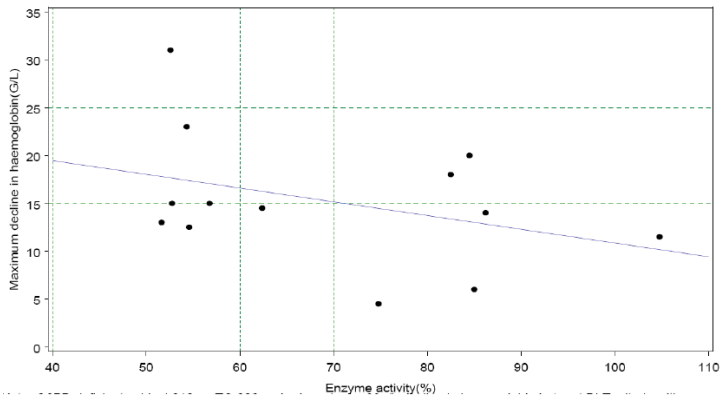
The median profiles for change from baseline Hb are presented in **Figure 1**. Compared to the profile for the G6PD normal, the cohorts of G6PD-deficient subjects who received TQ 300mg and PQ 15 mg had the greatest decline from baseline up to Day 10 before recovering. Hemoglobin declines in the G6PD deficient PQ cohort were more variable than in the G6PD deficient TQ 300 mg cohort but the maximum and median declines were broadly similar.

Figure 1 Change from Baseline Hemoglobin by G6PD status and Treatment Group (Pharmacodynamic Population)



As shown in **Figure 2**, there appears an apparent weak association between enzyme activity and maximum decline in Hb in the TQ 200 mg cohort of G6PD-deficient subjects, but no statistical testing was done due to the small sample size. The Applicant claimed that whilst those with enzyme activity lower than 70% had similar median declines in Hb, the range of decline in those with <70% activity was wider. Overall, the higher the G6PD activity, the smaller the hemoglobin decline observed i.e. there may be less hemolysis in subjects with >60% G6PD activity as compared to those with 40% to 60% activity.

Figure 2 Maximum Decline in Hemoglobin up to Day 14 and Baseline Enzyme Activity for G6PD-Deficient Subjects for TQ 200mg Cohort (Pharmacodynamic Population)



Reviewer's Comments: It is not clear why the Applicant only chose TQ 200 mg cohort to look at the association between enzyme activity and maximum decline in Hb. In addition, it is arbitrary to compare the range of Hb decline by using G6PD enzyme activity of 70% as a cutoff value based on the limited sample size.

Pharmacokinetics and Pharmacodynamics Relationship

With the limited data from subjects in this study, there was no clear correlation established between TQ exposure (Cmax or AUC) and maximum decline in Hb in either G6PD-deficient or G6PD-normal subjects. However, four of the five subjects with the greatest declines in Hb had the highest Cmax values. Nevertheless, a more than doubling of the Cmax observed in the TQ 300 mg cohort did not alter the magnitude of decline in Hb.

Safety Results

TQ, dosed with food, was well tolerated up to the 300 mg dose studied with no serious AEs and few AEs, none of which were attributed to the drug by the investigator. No subjects reported any clinical symptoms relating to their observed Hb decline.

REVIEWER'S ASSESSMENT

Study TAF 110027 assessed the hemolytic potential of TQ in healthy subjects with G6PD deficiency versus those subjects with normal G6PD activity. We concur with the Applicant's following conclusions:

- There was a dose dependent decline in hemoglobin from baseline in G6PD deficient subjects as compared to those with normal G6PD activity.
- Mean TQ AUC and Cmax values were generally similar for G6PD-normal and G6PD-deficient females.

However, it appears that this study did not provide sufficient evidence to identify a cutoff value of 70% G6PD enzyme activity to distinguish between G6PD deficient and G6PD normal subjects.

STUDY NO.: SB252263/015

An open-label study to determine the effect of TQ on the plasma pharmacokinetic profile of desipramine in healthy male and female volunteers

Date(s): 26 July 1999 – 4 November 1999
Sponsor: SmithKline Beecham
Testing Site: (b) (4)

Analytical Site
Sample Analysis Date(s): (b) (4)

METHODS

Study Design:

The study consisted of two treatment sessions; in the first treatment session, following an overnight fast, each subject received a single oral dose of desipramine 100 mg on Day 1 followed by a 7-day washout.

In the second treatment session, each subject received TQ 400 mg QD for 3 days from Day 8, 9 and 10, followed by an overnight fast prior to administration of a single oral dose of desipramine 100 mg, 12 hours after the last dose of TQ (i.e. in the morning of Day 11). Each dose of TQ was administered with food in the evening.

A dose of TQ 400 mg once daily (QD) for 3 days was chosen for this study because at the time, this was the anticipated loading dose of the prophylaxis regimen to be used in Phase III studies. Dosing for 3 days was required to rapidly achieve near steady state plasma levels and the interaction with desipramine was to be evaluated at maximal plasma levels of TQ.TQ in this clinical study was administered as a capsule formulation of 200 mg.

Assessments

Pharmacokinetic Assessments: Blood samples (~ 2.5 mL) for the determination of plasma concentrations of desipramine were collected pre-dose (0 hours), at 1 hour intervals until 10 hours post-dose, and at 12, 14, 24, 32, 48, 72 and 96 hours post-dose both on Days 1 and 11.

On the evening of Day 8, 9 and 10, a pre-dose blood sample was collected prior to the administration of TQ was administered for determining the minimum plasma concentration (Cmin). In addition, blood samples were collected pre- dose and at 24, 36, 60, 84 and 108 hours after the last dose of TQ, corresponding to 12, 24, 48, 72 and 96 hours after dosing with desipramine. Additional 2.5 mL samples were collected at bi-weekly intervals after the last (third) dose of TQ for 8 weeks, and a final sample was collected 9 weeks after the last dose of TQ.

Desipramine and TQ plasma concentration time data were analyzed by non-compartmental analysis. The reported sample times are the actual times of sample collection.

Analytical Methods: The analytical method, matrix, and lower limit of quantification (LLQ) values are summarized in **Table 1**. Plasma samples were assayed for desipramine using a method based on solvent extraction followed by gas chromatography using nitrogen-phosphorus detection. Quality control (QC) samples were assayed with each batch of samples against separately prepared calibration standards. Plasma samples were assayed for TQ using LC/MS/MS method.

Table 1. Bioanalytical Methods Summary

Analyte	Matrix	LLQ
Desipramine	Plasma	0.5 ng/mL
TQ	Plasma	2 ng/mL

Reviewer Comment: The bioanalytical methods are acceptable.

RESULTS AND CONCLUSIONS

Pharmacokinetic Results: The plasma concentration-time profiles of desipramine when administered alone and when administered with TQ appear similar. A summary of the PK parameters for desipramine alone and coadministration with TQ are presented in **Table 2.**

Table 2. Geometric Mean (CVb%) Desipramine Pharmacokinetic Parameters

Regimen		Cmax (ng/mL)	Tmax# (h)	AUC(0-∞) (ng.h/mL)	T½ (h)
Desipramine Alone	Mean	27.5	7.00	955	22.5
	SD	11.7	3.00 – 14.1	1115	14.5
Desipramine +	Mean	28.3	7.00	891	19.9
TQ	SD	11.7	3.00-10.00	979	10.4

= Tmax (median & range)

The statistical analyses provided the following overall comparison of AUC(0-∞) and Cmax between regimens for desipramine can be seen in **Table 3**.

Table 3. Summary of Results of Statistical Analysis of Primary Pharmacokinetic Parameters Comparison for Desipramine alone and Desipramine with TQ

Parameter	Comparison^	Ratio or Difference	90% C.I.*	CV% (within)
AUC(0-∞)	C : A	0.94	(0.89, 1.00)**	11.7
Cmax	C : A	1.04	(0.98, 1.10)	11.1

^ A : Desipramine alone; C : Desipramine + TQ

* Adjusted 90 % confidence interval (to account for the interim analysis)

** Confidence Interval 0.999 is rounded to 1.00

The arithmetic mean (SD) PK parameter estimates for TQ after administration of the last (third) 400 mg dose are summarized in **Table 4**. The Cmax for TQ ranged from 240 to 967 ng/mL.

Table 4. Arithmetic Mean Pharmacokinetic Parameter Estimates for TQ

Parameter (units)	Mean (SD)
AUC(0-∞) (µg.h/mL)	275 (80)
Cmax (ng/mL)	496 (162)
Tmax (h)*	24.0 (0.0-84.0)
T1/2 (h)	436 (95)

*Median (range)

Reviewer Comment: In this study, the TQ Cmax ranged from 244 to 967 ng/mL with a mean Cmax of 496 ng/mL, which overlapped with Cmax values following three consecutive once daily oral doses of 400 mg TQ observed in other studies.

REVIEWER'S ASSESSMENT

Based on the findings from this study, it appears that TQ is not an inhibitor of CYP2D6, and thus, is unlikely to affect the metabolism of other drugs that undergo biotransformation by CYP2D6.

STUDY NO.: SB252263/040

Evaluation of the Effect of TQ on the Metabolism of Multiple Cytochrome P-450 Substrates

Date(s): 25 July 2005– 21 November 2005
Sponsor: GlaxoSmithKline (GSK) R&D Ware, Hertfordshire, UK
Testing Site: (b) (4)
Analytical Site:
Sample Analysis Date(s): Could not locate this information from the CSR

OBJECTIVES

Primary

To characterize the effect of dosing of TQ (TQ) on the pharmacokinetics (PK) of a single oral dose of enzyme substrates midazolam (CYP3A4), flurbiprofen (CYP2C9) and caffeine (CYP1A2) in healthy volunteers.

RATIONALE

The purpose of this study was to investigate the in vivo potential for TQ to interact with substrates of CYP2C9, 3A4 and 1A2. Due to the long half-life of TQ, ranging from 15 – 35 days, the study was not designed as a randomized crossover study. To achieve relevant therapeutic concentrations of the drug during the study period, a loading dose was administered of TQ. The study utilized this approach, thereby achieving a pseudo steady state after only 3 days of dosing.

METHODS

Study Design: This was an open-label, two-period, non-randomized, crossover study. Each subject participated in 2 study sessions (**Table 1**) separated by a washout period of at least 7 days.

Table 1. Study Medication Administration Schedule

Session 1		
Study Day	**Study Drug, Dose**	
1	Midazolam, 5 mg	
2	"Multi-drug cocktail"	Flurbiprofen, 50 mg
		Caffeine, 200 mg
Session 2		
Study Day	**Study Drug, Dose**	
1-2	Tafenoquine 400 mg	
3	Tafenoquine 400 mg; Midazolam, 5 mg	
4[1]	"Multi-drug cocktail"	Flurbiprofen, 50 mg
		Caffeine, 200 mg
1. Tafenoquine was not coadministered with the multi-drug cocktail on Day 4 of Session 2.		

TQ was administered under fed condition in this study.

TQ (capsule) in this clinical study was supplied by GSK. Midazolam (solution), flurbiprofen (tablet), and caffeine (tablet) were supplied by the study site and the manufacturers for these were (b) (4) respectively.

Assessments

Pharmacokinetic Assessments: Nine blood samples (~2 mL) were collected for midazolam/1'-hydroxymidazolam PK analyses on Day 1 of Session 1 and Day 3 of Session 2 at designated times up to 24 hours post-dose.

Nine blood samples (~5 mL) for caffeine/paraxanthine and flurbiprofen PK analyses were collected on Day 2 of Session 1 and Day 4 of Session 2 at designated times up to 24 hours post-dose.

Pre-dose blood samples (~2.5 mL) were collected for TQ PK analysis on Days 1, 3, and 4 of Session 2.

Urine samples for 4'-hydroxyflurbiprofen PK analysis were collected on Day 2 of Session 1 and Day 4 of Session 2 just prior to 8 hour timepoint.

The following nomenclatures are used to describe the regimens administered during this clinical study and to perform the calculation on their geometric means.

Regimen A1: Midazolam 5 mg

Regimen A2: Flurbiprofen 50 mg, Caffeine 200 mg

Regimen B2: Midazolam 5 mg, TQ 400mg

Regimen B3: Flurbiprofen 50 mg + Caffeine 200 mg (post administration of TQ 400 mg)

Analytical Methods: PK samples were analyzed by validated HPLC-MS/MS. The assays were validated over the relevant concentration range. The performance of the bioanalytical methods is acceptable.

RESULTS AND CONCLUSIONS

Pharmacokinetic Results: A summary of the midazolam, 1'-Hydroxymidazolam, caffeine, paraxanthine, flurbiprofen and 4'-hydroxyflurbiprofen PK parameters along with the ratios of 1'Hydroxymidazolam/Midazolam and paraxanthine/caffeine are presented in **Table 2, 3, 4, 5, 6, 7, 8, and 9** respectively. The ratio of the primary and secondary PK parameters for the substrates of CYP3A4 (midazolam), CYP1A2 (caffeine), and CYP2C9 (flurbiprofen) with and without TQ are presented in **Table 10 and 11**.

Table 2. Geometric Mean (CVb%) Midazolam Pharmacokinetic Parameters

Session	Day	Regimen	AUC(0-∞) (ng·hr/mL)	AUC(0-t) (ng·hr/mL)	CL/F (L/hr)	Cmax (ng/mL)	tmax (hr)[1]	t½ (hr)
1	1	Midazolam 5 mg	77.5 (25.8)[2]	69.5 (28.0)[3]	64.8 (26.0)[2]	17.9 (48.4)[3]	0.53 (0.25-4.00)[3]	3.04 (40.6)[2]
2	3	Tafenoquine 400 mg + Midazolam 5 mg	68.5 (35.7)[2]	61.7 (35.8)[3]	73.5 (36.0)[2]	17.3 (38.7)[3]	0.50 (0.25-2.02)[3]	2.99 (51.6)[2]

1. Median (range)
2. N = 22
3. N = 25

Table 3. Geometric Mean (CVb%) 1'-Hydroxymidazolam Pharmacokinetic Parameters

Session	Day	Regimen	AUC(0-∞) (ng·hr/mL)	AUC(0-t) (ng·hr/mL)	CL/F (L/hr)	Cmax (ng/mL)	tmax (hr)[1]	t½ (hr)
1	1	Midazolam 5 mg	27.3 (41.8)[2]	22.0 (45.7)[3]	182 (41.2)[2]	6.66 (67.2)[3]	0.55 (0.25-4.00)[3]	2.49 (23.7)[2]
2	3	Tafenoquine 400 mg + midazolam 5 mg	21.6 (28.0)[2]	17.3 (35.5)[3]	231 (27.8)[2]	6.48 (39.1)[3]	0.50 (0.25-2.00)[3]	2.00 (38.6)[2]

1. Median (range)
2. N = 11; t½ and therefore AUC(0-∞) could only be determined in both sessions for 11 subjects.
3. N = 25

Table 4. Geometric Mean (CVb%) 1'-Hydroxymidazolam/Midazolam Ratios

Session	Day	Regimen	AUC(0-∞) Ratio	AUC(0-t) Ratio
1	1	Midazolam 5 mg	0.324 (28.6)[1]	0.317 (37.1)[2]
2	3	Tafenoquine 400 mg + midazolam 5 mg	0.283 (31.4)[1]	0.280 (40.4)[2]

1. N = 11; t½ and therefore AUC(0-∞) could only be determined in both sessions for 11 subjects.
2. N = 25

Table 5. Geometric Mean (CVb%) Caffeine Pharmacokinetic Parameters

Session	Day	Regimen	AUC(0-∞) (ng·hr/mL)	AUC(0-t) (ng·hr/mL)	CL/F (L/hr)	Cmax (ng/mL)	tmax (hr)[1]	t½ (hr)
1	2	Flurbiprofen 50 mg + Caffeine 200 mg	37177 (40.0)[2]	34759 (37.9)[2]	5.38 (40.1)[2]	4929 (21.9)[2]	1.00 (0.5-2.00)[2]	5.13 (35.1)[2]
2	4	Tafenoquine 400 mg + Flurbiprofen 50 mg + Caffeine 200 mg	37675 (40.9)[2]	35245 (38.2)[2]	5.31 (40.9)[2]	4671 (24.2)[2]	0.79 (0.48-2.00)[2]	5.31 (32.1)[2]

1. Median (range)
2. N = 24

Table 6. Geometric Mean (CVb%) Paraxanthine Pharmacokinetic Parameters

Session	Day	Regimen	AUC(0-t) (ng·hr/mL)	Cmax (ng/mL)	tmax (hr)[1]
1	2	Flurbiprofen 50 mg + Caffeine 200 mg	17733 (25.2)[2]	1161 (21.3)[2]	8.00 (4.08-12.08)[2]
2	4	Tafenoquine 400 mg + Flurbiprofen 50 mg + Caffeine 200 mg	18522 (28.1)[2]	1187 (21.0)[2]	8.00 (4.00-12.0)[2]

1. Median (range)
2. N = 24

Table 7. Geometric Mean (CVb%) Paraxanthine/Caffeine Ratios

Session	Day	Regimen	Concentration (8 hours post-dose) Ratio	Metabolic [AUC(0-t)] Ratio
1	2	Flurbiprofen 50 mg + Caffeine 200 mg	0.626 (37.5)[1]	0.510 (20.5)[1]
2	4	Tafenoquine 400 mg + Flurbiprofen 50 mg + Caffeine 200 mg	0.646 (37.2)[1]	0.526 (22.0)[1]

1. N = 24

Table 8. Geometric Mean (CVb%) Flurbiprofen Pharmacokinetic Parameters

Session	Day	Regimen	AUC(0-∞) (µg·hr/mL)	AUC(0-t) (µg·hr/mL)	CL/F (L/hr)	Cmax (µg/mL)	tmax (hr)[1]	t½ (hr)
1	2	Flurbiprofen 50 mg + Caffeine 200 mg	39.5 (30.9)[2]	37.2 (28.7)[2]	1.27 (30.8)[2]	6.69 (24.7)[2]	2.00 (0.5-4.00)[2]	5.09 (29.5)[2]
2	4	Tafenoquine 400 mg + Flurbiprofen 50 mg + Caffeine 200 mg	44.5 (31.3)[2]	41.5 (28.3)[2]	1.13 (31.3)[2]	6.53 (29.5)[2]	2.00 (0.5-6.07)[2]	5.88 (23.4)[2]

1. Median (range)
2. N = 24

Table 9. Arithmetic Mean (95% CI) Free 4'-Hydroxyflurbiprofen Formation Clearance

Session	Day	Regimen	CLform (mL/hr)
1	2	Flurbiprofen 50 mg + Caffeine 200 mg	21.5 (13.7, 29.4)[1]
2	4	Tafenoquine 400 mg + Flurbiprofen 50 mg + Caffeine 200 mg	15.8 (8.83, 22.8)[1]

1. N = 23

Table 10. Summary of Results of Statistical Analysis of Primary Pharmacokinetic Parameters

Parameter	Comparison of Interest	Point Estimate	90% CI	CVw%
Midazolam				
AUC(0-∞) (ng•hr/mL)[1]	B2 : A1	0.88	(0.83, 0.94)	12.1
AUC(0-t) (ng•hr/mL)[1]	B2 : A1	0.89	(0.84, 0.94)	12.1
Flurbiprofen				
AUC(0-∞) (µg•hr/mL)[1]	B3 : A2	1.13	(1.09, 1.16)	6.7
AUC(0-t) (µg•hr/mL)[1]	B3 : A2	1.11	(1.07, 1.16)	7.7
Total 4'-hydroxyflurbiprofen				
Formation clearance (mL/hr)[1]	B3 : A2	0.85	(0.77, 0.94)	19.6
Caffeine				
AUC(0-∞) (ng•hr/mL)[1]	B3 : A2	1.01	(0.98, 1.05)	7.4
AUC(0-t) (ng•hr/mL)[1]	B3 : A2	1.01	(0.98, 1.05)	7.2
Paraxanthine/caffeine plasma AUC ratio[1]	B3 : A2	1.03	(0.99, 1.07)	8.0
Paraxanthine/caffeine plasma 8 h Concentration ratio[1]	B3 : A2	1.03	(0.98, 1.09)	10.4

1. Point estimate represents the ratio of the adjusted geometric means between regimens

Regimen A1: Midazolam 5 mg
Regimen A2: Flurbiprofen 50 mg, Caffeine 200 mg
Regimen B2: Midazolam 5 mg, Tafenoquine 400mg
Regimen B3: Flurbiprofen 50 mg + Caffeine 200 mg (post administration of Tafenoquine 400 mg)

Table 11. Summary of Results of Statistical Analysis of Secondary Pharmacokinetic Parameters

Parameter	Comparison of Interest	Point Estimate	90% CI	CVw%
Midazolam				
Cmax (ng/mL)[1]	B2 : A1	0.97	(0.83, 1.13)	32.0
t½ (hr)[1]	B2 : A1	0.98	(0.89, 1.08)	18.8
CL/F (L/h)[1]	B2 : A1	1.13	(1.06, 1.21)	12.3
tmax (hr)[2]	B2 - A1	0.00	(-0.25, 0.23)	
1'-Hydroxymidazolam				
AUC(0-t) (ng•hr/mL)[1]	B2 : A1	0.78	(0.71, 0.87)	20.9
Cmax (ng/mL)[1]	B2 : A1	0.97	(0.80, 1.18)	40.8
tmax (hr)[2]	B2 - A1	-0.13	(-0.75, 0.13)	
1-Hydroxymidazolam/ Midazolam AUC(0-∞)[1]	B2 : A1	0.87	(0.78, 0.98)	15.14
1-Hydroxymidazolam/ Midazolam AUC(0-t)[1]	B2 : A1	0.88	(0.79, 0.98)	22.43
Flurbiprofen				
Cmax (µg/mL)[1]	B3 : A2	0.98	(0.91, 1.04)	13.9
t½ (hr)[1]	B3 : A2	1.15	(1.10, 1.21)	9.1
CL/F (L/h)[1]	B3 : A2	0.89	(0.86, 0.92)	6.7
tmax (hr)[2]	B3 - A2	0.50	(0.00, 1.25)	
Caffeine				
Cmax (ng/mL)[1]	B3 : A2	0.95	(0.89, 1.01)	13.6
t½ (hr)[1]	B3 : A2	1.03	(0.99, 1.08)	8.8
CL/F (L/h)[1]	B3 : A2	0.99	(0.95, 1.02)	7.4
tmax (hr)[2]	B3 - A2	0.00	(-0.01, 0.03)	

1. Point estimate represents the ratio of the adjusted geometric means between regimens
2. Point estimate represents median difference between regimens

Regimen A1: Midazolam 5 mg
Regimen A2: Flurbiprofen 50 mg, Caffeine 200 mg
Regimen B2: Midazolam 5 mg, Tafenoquine 400mg
Regimen B3: Flurbiprofen 50 mg + Caffeine 200 mg (post administration of Tafenoquine 400 mg)

REVIEWER'S ASSESSMENT

Based on the findings from this study, there is no clinically significant effect of TQ on the PK of substrates of CYP3A4, CYP1A2, and CYP2C9.

STUDY NO.: TAF106491

Safety, Tolerability, and Pharmacokinetic Study of Concomitant CQ and TQ in Healthy Volunteers

Date(s): 24 March 2009– 26 August 2009
Sponsor: GlaxoSmithKline (GSK) R&D Ware, Hertfordshire, UK
Testing Site: (b) (4)
Analytical Site

OBJECTIVES

The primary objectives were:

- To characterize the effect of TQ (TQ) on the pharmacokinetics (PK) of CQ (CQ) following multiple doses of each study medication.
- To characterize the effect of CQ on the PK parameters of TQ following multiple doses of each study medication administered concurrently.
- To assess the safety and tolerability of the concomitant administration of oral doses of TQ and CQ in healthy male and female adult subjects.

METHODS

Trial Design

Due to the long half-life of TQ (about 14-19 days) and CQ (> 1 month), the current study was a parallel-group design. This phase I study was divided into 2 parts.

Part 1. Part 1 was a three arm, open label pilot study to evaluate the safety and pharmacokinetics of a low dose CQ in combination with TQ.

Table 1. Part 1 Dosing Regimens

Part 1 Dosing Regimens (Cohort 1)									
	CQ/TQ Arm N=6			Control Arm (CQ alone) N=3			Control Arm (TQ alone) N=3		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
CQ	300mg	300mg	300mg	300mg	300mg	300mg			
TQ		450mg	450mg					450mg	450mg

Note: CQ was administered as pure free base

Part 2. Part 2 was a double-blind study to assess the drug-drug interaction, safety (including electrocardiogram [ECG] effects), tolerability and PK parameters of the CQ/TQ combination.

Table 2. Part 2 Dosing Regimens

Part 2 Dosing Regimens				
Cohort	N	Day 1	Day 2	Day 3
2	20	600mg CQ	600mg CQ / placebo TQ	300mg CQ/ placebo TQ
3	20	placebo CQ	placebo CQ / 450mg TQ	placebo CQ / 450mg TQ
4	20	600mg CQ	600mg CQ / 450mg TQ	300mg CQ / 450mg TQ

Note: CQ was administered as pure free base

Reviewer's Comments: The dose regimen of CQ from Part 2 is the same to the CQ doses that were used in the Phase 3 pivotal study (TAF112582 Part 2). However, the TQ dose tested in this study (450 mg on Day 2 and Day 3) is higher than the TQ dose (300 mg SD) used in the Phase 3 pivotal study which is the labeling proposed TQ dose. This is acceptable since a higher than therapeutic doses for TQ would provide maximal TQ drug exposure to examine the effect of TQ on the PK of CQ.

Assessments

Pharmacokinetic Assessments

Thirty-two Blood samples were collected for pharmacokinetic analyses of TQ, CQ, and desethylCQ (CQ metabolite) from Day 2 to Day 42 following oral doses of TQ alone, CQ alone, or TQ and CQ concomitantly.

Plasma TQ, CQ, and desethylCQ metabolite concentration-time data were analyzed by non-compartmental methods.

Analytical Methods:

Analyses of TQ, CQ, and desethylCQ plasma concentrations were conducted using a validated analytical method based on protein precipitation followed by HPLC-MS/MS. The assay was validated over the TQ, CQ, and desethylCQ concentration range 2 to 3000 ng/mL in human plasma.

Reviewer's Comments: The performance of the bioanalytical methods for plasma TQ, CQ, and desethylCQ has been evaluated by the Applicant. The bioanalytical methods are acceptable.

RESULTS AND CONCLUSIONS

Seventy healthy volunteers completed the study (37 males and 33 females; age range 18-55 years). TQ and CQ co-administration was well tolerated triggering Part 2 of the study.

Pharmacokinetic Results

TQ

The summary PK parameters for TQ are listed in **Table 3**. The change in TQ exposure with CQ coadministration estimated in Part 2 of the study is listed in **Table 4**.

Table 3. Plasma TQ PK Parameters from Part 2

Summary of Selected Plasma Tafenoquine Pharmacokinetic Parameters: Part 2[1]								
Regimen	N	Day	AUC(0-t) (ng·h/mL)[2]	AUC(0-24) (ng·h/mL)	AUC(0-∞) (ng·h/mL)[3]	Cmax (ng/mL)	t1/2 (h)	tmax (h)[4]
TQ	20	2	265418 (29)	6279 (41)	299829 (30)[5]	370 (43)	NC	12.0 (5 - 24)
		3	NA	13294 (31)	NA	767 (22)	366 (25)[5]	7.0 (5 - 18)
TQ/CQ	18	2	260853 (23)	7755 (28)	293622 (24)	513 (33)	NC	10.5 (5 - 18)
		3	NA	14842 (22)	NA	869 (25)	389 (20)	5.0 (5 - 18)

Regimen:
TQ = Tafenoquine only (450 mg on Days 2 and 3)
TQ/CQ = Tafenoquine (450 mg) administered concomitantly with Chloroquine (600mg and 300 mg) on Days 2 and 3.

1. Geometric mean (CVb%)
2. AUC(0-t) = AUC(0-24 from Day 2 + AUC(0-t) from Day 3
3. AUC(0-∞) = AUC(0-24) from Day 2 + AUC(0-∞) from Day 3
4. Median (range)
5. n = 19

NA = Not applicable
NC = Not calculated

Table 4. Change in TQ Plasma PK Parameters when Administered with and without CQ: Part 2

Statistical Assessment of Tafenoquine PK Parameters: Part 2					
Parameter	Comparison	Ratio	90% CI	CVw (%)	CVb (%)
AUC(0-∞)[1,3]	TQ/CQ:TQ	0.98	(0.84, 1.14)	-	27.4
AUC(0-t)[2]	TQ/CQ:TQ	0.98	(0.85, 1.13)	-	26.4
AUC(0-24)	Day 2 TQ/CQ:TQ	1.24	(1.04, 1.46)	12.9	-
	Day 3 TQ/CQ:TQ	1.12	(0.94, 1.32)		
Cmax	Day 2 TQ/CQ:TQ	1.38	(1.17, 1.64)	24.2	-
	Day 3 TQ/CQ:TQ	1.13	(0.96, 1.34)		
t1/2[3]	Day 3 TQ/CQ:TQ	1.06	(0.94, 1.20)	-	22.9
Tmax[4]	Day 2 TQ/CQ-TQ	0	(-4.0, 2.0)	-	-
	Day 3 TQ/CQ-TQ	0	(-2.0, 0.0)		

Regimen:
TQ (n= 18) = Tafenoquine only (450mg on Days 2 and 3)
TQ/CQ (n = 20)= Tafenoquine (450mg) administered concomitantly with Chloroquine (300mg and 600mg) on Days 2 and 3, respectively.

1. AUC(0-∞)= AUC(0-24) from Day 2 + AUC(0-∞) from Day 3
2. AUC(0-t) = AUC(0-24) from Day 2 + AUC(0-t) from Day 3
3. n = 19 for TQ cohort
4. Tmax ratios are the estimated median difference

Reviewer's Comments: TQ exposures, Cmax and AUC(0-24), increased by 38% and 24%, respectively, when TQ was co-administered with CQ (600 mg) on Day 2. The extent in the increase of TQ exposure was reduced on Day 3 probably because that CQ dose was lowered to 300 mg on Day 3. Given the acceptable safety profiles of TQ at the therapeutic dose (300 mg) when co-administration with CQ in the Phase 3 studies, we agree that there is no clinically significant pharmacokinetic interaction with concomitant administration of TQ and CQ.

CQ

The summary PK parameters for CQ are listed in **Table 5**. The change in CQ exposure with TQ co-administration estimated in Part 2 of the study is listed in **Table 6**. The results demonstrate lack of clinically significant impact of TQ on CQ exposure when co-administered.

Table 5. Plasma CQ PK Parameters from Part 2

Summary of Selected Plasma Chloroquine Pharmacokinetic Parameters: Part 2[1]								
Regimen	N	Day	AUC(0-t) (ng·h/mL)[2]	AUC(0-24) (ng·h/mL)	AUC(0-∞) (ng·h/mL)[3]	Cmax (ng/mL)	t1/2 (h)	tmax (h)[4]
CQ	18	2	25194 (30)	4793 (35)	26195 (29)	374 (42)	NC	5.0 (1 - 12)
		3	NA	4087 (31)	NA	252 (38)	207 (30)	5.0 (0 - 9)
CQ/TQ	18	2	25011 (33)	4618 (24)	26082 (32)	333 (28)	NC	5.0 (2 - 15)
		3	NA	4315 (27)	NA	261 (30)	193 (34)	5.0 (2 - 15)

Regimen:
CQ = Chloroquine only (600 mg on Days 1 and 2 and 300 mg on Day 3)
CQ/TQ = Chloroquine (600 and 300 mg) administered concomitantly with Tafenoquine (450 mg) on Days 2 and 3.

1. Geometric mean (CVb%)
2. AUC(0-t) = AUC(0-24) from Day 2 + AUC(0-t) from Day 3
3. AUC(0-∞) = AUC(0-24) from Day 2 + AUC(0-∞) from Day 3
4. Median (range)

NA = Not applicable
NC = Not calculated

Table 6. Change in CQ Plasma PK Parameters when Administered With and Without TQ: Part 2

Statistical Assessment of Chloroquine PK Parameters: Part 2					
Parameter	Comparison	Ratio	90% CI	CVw (%)	CVb (%)
AUC(0-∞)[1]	CQ/TQ:CQ	1.00	(0.84, 1.18)	--	30.2
AUC(0-t)[2]	CQ/TQ:CQ	0.99	(0.83, 1.18)	--	31.6
AUC(0-24)	Day 2 CQ/TQ:CQ	0.96	(0.82, 1.13)	9.23	--
	Day 3 CQ/TQ:CQ	1.06	(0.90, 1.24)		
Cmax	Day 2 CQ/TQ:CQ	0.89	(0.74, 1.08)	21.4	--
	Day 3 CQ/TQ:CQ	1.04	(0.86, 1.25)		
t1/2	Day 3 CQ/TQ:CQ	0.94	(0.78, 1.12)	--	32.1
Tmax[3]	Day 2 CQ/TQ:CQ	0.0	(0.0, 2.0)	--	--
	Day 3 CQ/TQ:CQ	0.0	(0.0, 2.0)		

Regimen:
CQ (n= 18) = Chloroquine only (600mg on Days 1 and 2 and 300mg on Day 3)
CQ/TQ (n = 18) = Chloroquine (600 and 300mg) administered concomitantly with Tafenoquine (450mg) on Days 2 and 3.

1. AUC(0-∞)= AUC(0-24) from Day 2 + AUC(0-∞) from Day 3
2. AUC(0-t) = AUC(0-24) from Day 2 + AUC(0-t) from Day 3
3. Tmax ratios are the estimated median difference

DesethylCQ

The summary PK parameters for desethylCQ are listed in **Table 7**.

Table 7. Plasma DesethylCQ PK Parameters from Part 2

Summary of Selected Plasma Desethylchloroquine Pharmacokinetic Parameters: Part 2[1]

Regimen	N	Day	AUC(0-t) (ng·h/mL)[2]	AUC(0-24) (ng·h/mL)	AUC(0-∞) (ng·h/mL)[3]	Cmax (ng/mL)	t1/2 (h)	tmax (h)[4]
CQ	18	2	4688 (57)	854 (53)	5385 (66)[5]	63.9 (50)	NC	5.0 (2 - 24)
		3	NA	816 (47)	NA	51.5 (48)	119 (79)[5]	5.0 (0 - 24)
CQ/TQ	18	2	5073 (66)	761 (45)	6422 (57)[6]	54.0 (43)	NC	5.0 (3 - 18)
		3	NA	791 (46)	NA	47.2 (44)	143 (44)[6]	5.0 (1 - 24)

Regimen:
CQ = Chloroquine only (600 mg on Days 1 and 2 and 300 mg on Day 3)
CQ/TQ = Chloroquine (600 and 300 mg) administered concomitantly with Tafenoquine (450 mg) on Days 2 and 3.

1. Geometric mean (CVb%)
2. AUC(0-t) = AUC(0-24) from Day 2 + AUC(0-t) from Day 3
3. AUC(0-∞) = AUC(0-24) from Day 2 + AUC(0-∞) from Day 3
4. Median (range)
5. n = 12
6. n = 11

NA = Not applicable
NC = Not calculated

REVIEWER'S ASSESSMENT

Based on the PK results from the pivotal Part 2 portion of this study, there appears to be a short term minor increase in TQ Cmax when TQ was co-administered with CQ with no significant effect on the full PK profile (AUC(0-∞) and t1/2). TQ had no significant effect on the PK of CQ and desethylCQ. In addition, the safety profiles of TQ at the therapeutic dose (300 mg) when co-administer with CQ are acceptable in the Phase 3 studies. Taken together, we agree that there is no clinically significant pharmacokinetic interaction with concomitant administration of TQ and CQ.

STUDY NO.: 200951

A five-cohort, randomized, open-label, parallel-group study to evaluate the pharmacokinetics of a single dose of TQ 300mg when co-administered with the artemisinin-based combination therapies (ACT), artemether + lumefantrine (AL) and dihydroartemisinin + piperaquine tetraphosphate (DHA+PQP).

Date(s): 31 July 2014– 08 August 2015
Sponsor: GlaxoSmithKline (GSK) R&D Ware, Hertfordshire, UK
Testing Site: (b) (4)
Analytical Site:

OBJECTIVES

The primary objectives and endpoints of this study are listed below:

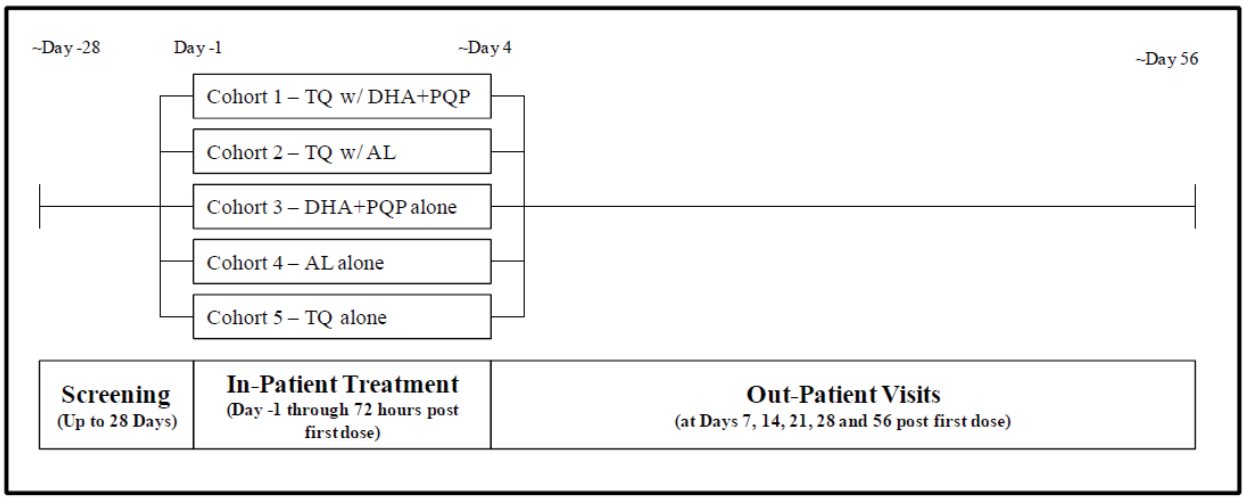
Objectives	Endpoints
Primary	
To characterize the effects of: • 300 mg single dose tafenoquine (TQ) on the pharmacokinetics of DHA+PQP according to the prescribed dose when co-administered. • 300 mg single dose TQ on the pharmacokinetics of AL according to the prescribed dose when co-administered. • DHA+PQP according to the prescribed dose when co-administered with 300 mg single dose of TQ on the pharmacokinetics of TQ. • AL according to the prescribed dose when co-administered with 300 mg single dose of TQ on the pharmacokinetics of TQ.	Pharmacokinetic endpoints included • Ratios of geometric mean (90% confidence interval [CI]) for DHA+PQP area under the concentration-time curve (AUC) and maximum observed concentration (C_{max}) for treatment groups TQ + DHA+PQP vs. DHA+PQP. • Ratios of geometric mean [90% CI] for A/DHA/L AUC and C_{max} for treatment groups TQ + AL vs AL. • Ratios of geometric mean [90% CI] for TQ AUC and C_{max} for treatment groups TQ + DHA+PQP vs TQ. • Ratios of geometric mean [90% CI] for TQ AUC and C_{max} for treatment groups TQ + AL vs TQ. *Note*: For all comparisons - AUC from 0 to Last Nonzero Concentration ($AUC_{[0-t]}$) and/or AUC from 0 to infinity ($AUC_{[0-\infty]}$) was calculated (as data permitted).

METHODS

Trial Design

This was a single-center, 5-cohort, randomized open-label, parallel-group study in healthy volunteer subjects. The study design is represented schematically in **Figure 1**.

Figure 1. Study Design – 5 Cohort, Parallel-Group



A parallel-group design was selected for this study due to the long half-life of TQ (about 15-19 days) and the non-artemisinin components of the comparator drugs (i.e., piperaquine half-life ~22 days and lumefantrine half-life ~5 days). Open-label dosing was chosen as blinding would have no effect on the primary endpoint for this study which is changes in: AUC(0-t) and/or AUC(0-∞), and Cmax.

The dosing regimens are described in the **Table 1**. This study was designed to understand the potential interaction between TQ and two commonly prescribed ACTs: DHA-piperaquine and artemether-lumefantrine. Therefore, the dosing schedule was based around likely real world use of the drugs (i.e. PK parameters were centered around the third day of dosing of the ACT) rather than a more standard single dose DDI study design. In addition, the DHA-PQP was given in a fed state which potentially will have led to higher exposures particularly of PQP than if given in the fasted state.

Table 1. Dosing Regimens for Study 200951

Cohort	N[a]	Day1	Day 2	Day 3
TQ + DHA/PQP	24	TQ (300 mg) DHA/PQP (320/40 mg)	DHA/PQP (320/40 mg)	DHA/PQP (320/40 mg)
TQ + AL	24	TQ (300 mg) AL (120/20 mg) at 0 h and 8 h	AL (20/120 mg) at 24 h and 36 h	AL (20/120 mg) at 48 h and 60 h
DHA/PQP alone	23	DHA/PQP (320/40mg)	DHA/PQP (320/40 mg)	DHA/PQP (320/40 mg)
AL alone	22	AL (120/20 mg) at 0 h and 8 h	AL (20/120 mg) at 24 h and 36 h	AL (20/120 mg) at 48 h and 60 h
TQ alone	24	TQ (300 mg)		

Abbreviations: AL= artemether + lumefantrine; DHA/PQP = dihydroartemisinin + piperaquine tetraphosphate; TQ = tafenoquine

a. Number of subjects who contributed to PK parameter analysis

DHA/PQP and AL administered according to their labels

Reviewer's Comments: The Applicant indicated in the footnote of Table 1 that AL and DHA/PQP were dosed in this study according to the labels for AL (COARTEM®) and DHA/PQP (EURARTESIM®). However, the dosing information provided in Table 1 is not consistent with the dose regimens in these labels. As a response to our information request to clarify the dosing of AL and DHA/PQP, the Applicant confirmed that the dosing regimen for COARTEM® and EURARTESIM® in the study 200951 in the mono and TQ combination arms was administered in complete accordance of their recommended prescribing information (PI) as listed in Table 2 and Table 3.

Table 2: AL (COARTEM®) Dosing Regimen in Study 200951

Body Weight (kg)	Drug Administration Time (hrs)	Study Day	Label Recommended COARTEM Dosing Regimen	COARTEM Dosing Regimen in Study 200951
≥35 kg	0	1	4 tablets	4 tablets
	8		4 tablets	4 tablets
	24	2	4 tablets	4 tablets
	36		4 tablets	4 tablets
	48	3	4 tablets	4 tablets
	60		4 tablets	4 tablets

1. The dosing regimen for COARTEM was same in the COARTEM mono and COARTEM®+tafenoquine combination arms
2. All subjects in Study 200951 had body weight between 36 and 100 kg
3. Each COARTEM tablet contains 20 mg artemether and 120 mg lumefantrine.
4. Dosing schedule described in Table 24 of 200951 clinical pharmacology study report.

Table 3: DHA/PQPV (EURARTESIM®) Dosing Regimen in Study 200951

Body weight (kg)	Drug Administration Time (hrs)	Study Day	Label Recommended EURARTESIM Dosing regimen	EURARTESIM Dosing Regimen in Study 200951
36 to <75	0	1	3 tablets	3 tablets
	24	2	3 tablets	3 tablets
	48	3	3 tablets	3 tablets
75 to 100	0	1	4 tablets	4 tablets
	24	2	4 tablets	4 tablets
	48	3	4 tablets	4 tablets

1. The dosing regimen for EURARTESIM was same in the EURARTESIM mono and EURARTESIM+tafenoquine combination arms.
2. All subjects in Study 200951 had body weight between 36 and 100 kg
3. Each film-coated EURARTESIM tablet contains 40 mg dihydroartemisinin and 320 mg piperaquine tetraphosphate.
4. Dosing schedule described in Table 24 of 200951 clinical pharmacology study report.

TQ, DHA/PQP, and AL were all administered under fed condition in this study.

Assessments

Pharmacokinetic Assessments

Thirteen to Thirty-Four Blood samples (number of samples varied across cohorts) were collected at designated times from pre-dose to 56-days post first dose to characterize exposure of TQ, ACT components and their relevant metabolites.

Analytical Methods:

Plasma samples were analyzed for TQ, Piperaquine, Dihydroartemisin, Artemether or Lumefantrine by using validated analytical methods based on protein precipitation or liquid-liquid extraction, followed by HPLC or UHPLCMS/ MS analysis. The lower limit of quantification (LLQ) and higher limit of quantification (HLQ) for TQ, Dihydroartemisin, Artemether, Piperaquine and Lumefantrine was 2-3000 ng/mL, 1-2000 ng/mL, 5-2000 ng/mL, 4-2000 ng/mL and 2-4000 ng/mL respectively using a 25 µL, 125 µL, 125 µL, 100 µL or 50 µL aliquot of EDTA plasma respectively.

Reviewer's Comments: The performance of the bioanalytical methods for plasma TQ, Piperaquine, Dihydroartemisin, Artemether or Lumefantrine has been evaluated by the Applicant. The bioanalytical methods are acceptable.

RESULTS AND CONCLUSIONS

120 subjects were enrolled equally across the 5 arms (cohorts) in the study. Baseline characteristics were similar. Mean age was 35 to 40 years old and 71-88% men per group.

Pharmacokinetic Results

TQ

A summary of selected parameters for TQ following administration TQ+DHA/PQP, TQ+ AL or TQ alone are presented in Table 4.

Table 4. Summary of Selected Plasma TQ Pharmacokinetic Parameters

Actual Treatment	n	C_{max} (ng/mL)[1]	t_{max} (h)[2]	$AUC_{(0-\infty)}$ (h*ng/mL)[1]	$AUC_{(0-t)}$ (h*ng/mL)[1]	$t_{1/2}$ (h)[1]
TQ+DHA/PQP (N=24)	24	275 (21.2)	6.0 (6-23)	109334 (22.6)	93809 (20.5)	484 (18.7)
TQ + AL (N=24)	24	210 (19.5)	12.1 (2-60)	101022 (29.2)	90419 (26.3)	390 (17.8)
TQ (N=24)	24	200 (20.0)	12.1 (6-72)	97196 (24.1)	88284 (22.7)	375 (13.5)

[1]geometric mean (%CVb)
[2]median (range)

Reviewer's Comments: Comparing to TAF110027 (G6PD) Study that also tested TQ at 300 mg under fed condition, AUC(0-∞) is comparable to that observed from TAF110027 Study while Cmax is lower in this study (200 ng/mL vs 350 ng/mL from TAF110027 Study). The reason is not clear while the subject number for TAF110027 Study is small (N=6).

Dihydroartemisinin

A summary of selected parameters for DHA following administration DHA/PQP, TQ+DHA/PQP, AL (as metabolite of AL), or TQ+ AL (as metabolite of AL) are presented in **Table 5**.

Table 5. Summary of Selected Plasma Dihydroartemisinin Pharmacokinetic Parameters

Actual Treatment	n (n for $t_{1/2}$ if different)	C_{max} (ng/mL)[1]	t_{max} (h)[2]	$AUC_{(0-t)}$ (h*ng/mL)[1]	$AUC_{(0-tau)}$ (h*ng/mL)[1]	$t_{1/2}$ (h)[1]
DHA/PQP (N=23)	23	278 (45.0)	2.0 (1-6)	750 (36.2)	758 (35.9)	1.6 (30.5)
TQ+DHA/PQP (N=24)	23	263 (56.4)	2.0 (1-6)	749 (50.7)	761 (51.2)	1.7 (42.1)
AL (N=22)	22	106 (48.2)	2.0 (1-8)	299 (41.9)	300 (41.2)	2.2 (30.7)
TQ+AL (N=24)	22 (21)	87 (58.4)	1.9 (2-6)	239 (51.1)	227 (48.4)	1.8 (34.9)

[1]geometric mean (%CVb)
[2]median (range)

Piperaquine

A summary of selected parameters for Piperaquine following administration DHA/PQP or TQ+DHA/PQP are presented in **Table 6**.

Table 6. Summary of Selected Plasma Piperaquine Pharmacokinetic Parameters

Actual Treatment	n	C_{max} (ng/mL)[1]	t_{max} (h)[2]	$AUC_{(0-t)}$ (h*ng/mL)[1]	$AUC_{(0-tau)}$ (h*ng/mL)[1]	$t_{1/2}$ (h)[1]
DHA/PQP (N=23)	23	928 (30.5)	4.0 (3-8)	37358 (33.2)	9816 (27.6)	382 (104)
TQ+DHA/PQP (N=24)	24	841 (42.2)	4.0 (3-8)	35660 (31.7)	9207 (32.5)	360 (75.4)

[1]geometric mean (%CVb)
[2]median (range)

Artemether

A summary of selected parameters for Artemether following administration AL alone or TQ+AL are presented in **Table 7**. According to the Applicant, the AUC(0-tau) was calculated for only 12 of 22 subjects dosed with AL and 5 of 24 subjects dosed with TQ+AL. The extremely short t1/2 (~2 hrs) of Artemether makes it difficult to extrapolate the AUC(0-tau). In this case the AUC(0-t) after last dose was a better comparison to study the effect of TQ on artemether PK. The estimates for artemether AUC(0-t) in both groups, AL and TQ+AL, were comparable to literature reported estimates.

Table 7. Summary of Selected Plasma Artemether Pharmacokinetic Parameters

Actual Treatment	n [n for $t_{1/2}$ and $AUC_{(0-tau)}$]	C_{max} (ng/mL)[1]	t_{max} (h)[2]	$AUC_{(0-t)}$ (h*ng/mL)[1]	$AUC_{(0-tau)}$ (h*ng/mL)[1]	$t_{1/2}$ (h)[1]
AL (N=22)	22 (12)	22.4 (73.2)	2.0 (1-8)	38.0 (246.3)	103 (68.6)	2.0 (88.8)
TQ+AL (N=24)	21 (5)	23.2 (86.4)	2.0 (1-6)	38.8 (177.3)	186 (45.1)	1.5 (36.2)

[1]geometric mean (%CVb)
[2]median (range)

Lumefantrine

A summary of selected parameters for Lumefantrine following administration AL or TQ+AL are presented in **Table 8**.

Table 8. Summary of Selected Plasma Lumefantrine Pharmacokinetic Parameters

Actual Treatment	n	C_{max} (ng/mL)[1]	t_{max} (h)[2]	$AUC_{(0-t)}$ (h*ng/mL)[1]	$AUC_{(0-tau)}$ (h*ng/mL)[1]	$t_{1/2}$ (h)[1]
AL (N=22)	22	19054 (42.2)	4.0 (0-12)	817542 (57.1)	176945 (50.5)	165 (36.1)
TQ+AL (N=24)	22	20445 (50.8)	5.9 (0-12)	1043185 (64.3)	196499 (53.2)	198 (21.7)

[1]geometric mean (%CVb)
[2]median (range)

Exposure ratios on Co-administration of ACTs with TQ

Table 9 lists the point estimates and 90% CI of the geometric least squares mean ratios for the AUC0-tau (for DHA, PQP, AL), AUC(0-∞) (for TQ), AUC0-t and Cmax for all the analytes, i.e. dihydroartemisinin, piperaquine lumefantrine, artemether and TQ on co-administration of AL+TQ, DHA/PQP +TQ versus administering AL, DHA/PQP and TQ alone.

Table 9. Change in PK Parameters of TQ and ACT Components on Co-administration or Given Alone

Analyte	Treatment comparison	Ratio of LS Geometric Means – Point Estimate (90% Confidence Interval)		
		C_{max} (ng/mL)	$AUC_{(0-t)}$ (h*ng/mL)	$AUC_{(0-tau)}$ (h*ng/mL)
DHA	(TQ+DHA/PQP vs DHA/PQP)	0.95 (0.75, 1.20)	1.00 (0.81, 1.23)	1.00 (0.82, 1.24)
DHA	(TQ+AL vs AL)	0.84 (0.65, 1.09)	0.82 (0.65, 1.02)	0.77 (0.62, 0.96)
PQP	(TQ+DHA/PQP vs DHA/PQP)	0.91 (0.76, 1.08)	0.95 (0.82, 1.11)	0.94 (0.81, 1.08)
TQ	(TQ+DHA/PQP vs TQ)	1.38 (1.25, 1.52)	1.06 (0.96, 1.18)	1.12 (1.01, 1.26)
TQ	(TQ+AL vs TQ)	1.04 (0.95, 1.15)	1.03 (0.92, 1.16)	1.05 (0.93, 1.20)
Artemether	(TQ+AL vs AL)	1.03 (0.71, 1.49)	1.03 (0.52, 2.04)	1.81 (1.06, 3.10)
Lumefantrine	(TQ+AL vs AL)	1.08 (0.86, 1.36)	1.29 (0.97, 1.73)	1.13 (0.87, 1.45)

DHA: Dihydroartemisinin; PQP: Piperaquine tetraphosphate; TQ: TQ; AL: Artemether + Lumefantrine

Safety Results

TQ and the ACTs studied appear to be safe following co-administration. Adverse events were seen less frequently when TQ was dosed on its own (13%) than when co-dosed with either

DHA/PQP or AL (33-38%). There was no evidence that the addition of TQ to ACT increased the number of patients experiencing adverse events of any cause compared with ACTs alone: DHA/PQP (58%) versus TQ+DHA/PQP (38%); AL alone (54%) versus TQ+AL (33%). The only adverse event seen >10% in any group was headache which appeared to be equally distributed. Otherwise, TQ co-administration with ACT compared with administration of ACT alone did not result in an increase in AEs, and did not affect the nature of the AEs experienced.

REVIEWER'S ASSESSMENT

This study investigated the effects of a 300 mg single dose of TQ on the pharmacokinetics of daily doses of DHA+PQP and AL and vice versa.

Co-administration of DHA/PQP increased TQ AUC(0-∞) and Cmax by 12% and 38%, respectively. However, the TQ geometric mean Cmax (274.7 ng/ml) at 300 mg observed following DHA/PQP co-administration in this study was still well below that observed for 600 mg TQ (422 ng/ml) in the thorough QT study, so the increased exposure to TQ is likely to be of no clinical concern in G6PD normal subjects.

Concomitant administration of TQ with AL reduced the exposure of the dihydroartemisinin (metabolite of artemether) by 23% and 16% for AUC(0-tau) and Cmax, respectively. Considering that these changes are minor and the large variability was observed in the PK data of this metabolite, we agree with the conclusion from the Applicant that this change was not considered clinically significant.

Taken together, we agree that there are no clinically significant PK interactions with concomitant administration of TQ and ACTs and no dose adjustment was deemed necessary for co-administration of ACTs with TQ.

15.5. Clinical Microbiology Appendices

15.5.1. Activity in nonhuman primates

The following is the summary of nonclinical studies supporting activity of TQ in nonhuman primates infected with (a) erythrocytic parasites of *P. vivax*, (b) erythrocytic parasites of *P. cynomolgi*, and (c) sporozoites of *P. cynomolgi.*

***Plasmodium* species/ strain (Reference)**	**Study summary**
Infected with parasitized erythrocytes (suppressive activity)	
P. vivax / Chesson (Study report no. 2016N298150_00)	Panamanian monkeys (Aotus trivirgatus), were infected IV with 5 x 10^6 parasitized erythrocytes of the Chesson strain that was sensitive to CQ, pyrimethamine, and quinine. TQ was administered by gastric intubation for 3 days; time of treatment initiation was not specified. Giemsa stained blood smears were prepared daily to evaluate parasitemia. Once parasitemia had cleared, blood films were made and examined twice weekly until a total of 100 negative days had been recorded. If recrudescence occurred, blood films were obtained daily. The results show variability in the activity of TQ from animal to animal. At a dose between 1.0, 4.0, 16.0, and 32.0 mg/kg for 3 days, TQ was effective in reducing parasitemia. However, cures were reported at a dose of ≥16 mg/kg for 3 days.
P. vivax / AMRU-1 (Cooper et al., 1994)	Splenectomized *Aotus* monkeys were infected IV with 5 x 10^5 parasitized erythrocytes of a CQ resistant (AMRU-1) strain of *P. vivax* that was adapted in monkeys and previously isolated from an Australian Army serviceman who acquired the infection in Papua New Guinea. Thick and thin blood smears were prepared daily to measure parasitemia. All the six monkeys were parasitemic by Day 7 of inoculation. When the infections were established, with parasite densities >500/mm^3, the monkeys were treated orally with TQ (3 monkeys were administered 0.8 mg base/kg/d for 3 days and 3 received 3.2 mg base/kg/d for 3 days). The results show that the activity of TQ was slow and higher dose of TQ was more effective in decreasing parasitemia. Recrudescence was observed on Day 107 in one monkey treated with the low dose of TQ; this monkey had the slowest clearance of the parasites.
P. vivax / AMRU-1 (Obaldia et al., 1997)	Rhesus monkeys were infected IV with 5 x 10^6 erythrocytic parasites of a CQ resistant stain (AMRU 1) of *P. vivax*. The experimental design was same as summarized above (Cooper et al., 1994[31]). The results show that treatment with TQ at a dose of 3 mg/kg for 3 days was effective in suppressing parasitemia; however, recrudescence occurred between days 15 and 25. Higher dose (9 and 36 mg/kg) of TQ were effective in curing animals. Low dose (0.9 mg/kg) TQ in combination with CQ (30 mg/kg) were suppressing parasitemia but animals were not cured. CQ alone was not effective.
P. cynomolgi/B (Puri and Dutta, 2003)	Rhesus monkeys were infected IV with 10^5 parasitized erythrocytes and blood smears were prepared daily to determine parasitemia. Oral treatment with TQ was initiated for 7 days when parasitemia reached approximately 5000/mm^3. Monkeys were followed until Day 70 after the end of treatment. Monkeys, which did not show recrudescence through Day 70, were recorded as cured. Monkeys, which developed recrudescence within 30 days after the end of treatment, were retreated with the other anti-malarial drug or the next higher dose of the same agent upon attaining the required parasitemia level. It is noted that there was a rise in parasitemia 24 to 48 hours after the first dose. The results show that treatment with TQ at doses of 0.32 mg/kg/day and 1 mg/kg/day was

[31] Cooper RD, Milhous WK, and Rieckmann KH. The efficacy of WR238605 against the blood stages of a chloroquine resistant strain of *Plasmodium vivax. Trans Roy Soc Trop Med Hyg* (1994) 88: 691-692.

***Plasmodium* species/ strain (Reference)**	**Study summary**
	effective in clearing parasitemia. However, recrudescence occurred in all the monkeys treated with the 0.3 mg/kg/day dose and 3 of the 12 monkeys treated with the 1 mg/kg/day dose. The highest dose (3.2 mg/kg/day) tested was effective in clearing parasitemia and no recrudescence was observed up to Day 70. PQ, at the same doses was not effective, in preventing recrudescence.
Infected with sporozoites (Pre- and post-exposure: causal prophylaxis)	
P. cynomolgi / M (DiTusa et al., 2014)	Rhesus monkeys were infected IV with $4.7x10^4$ to $6x10^5$ sporozoites of the M strain of *P. cynomolgi*. Animals were treated orally for 3 days (Days -0, 0, +1) with TQ and other drugs. Efficacy was evaluated by blood smears in which parasitemia on thick and thin smears was assessed daily from Day 7 through Day 21, then 3 times per week for 4 weeks, then twice per week until Day 100 after the last day of treatment. Causal prophylaxis was defined as the absence of parasitemia up to Day 100 post-inoculation. The results show that TQ at a dose of 0.95 mg/kg was not effective in curing the animals although patency was delayed by 2 to 3 days. A higher dose (6 mg/kg) of TQ was effective in curing the monkeys. The number of monkeys in each group is small (n=2).
P. cynomolgi bastianelli (Study report no. 2016N298122_00)	Rhesus monkeys were infected IV with sporozoites (inoculum concentration not specified) and treated orally with TQ on Days -1, 0, and 1. Blood smears are examined from Day 7 until Day 70 to observe patency. Primary peak parasitemia was obtained 7-10 days after patency in untreated control monkeys. Preliminary experiments were conducted using 0.95 mg/kg administered on Days -2, -1 or 0 of sporozoite challenge. Patency was successfully prevented in only one animal which had been given the drug on Day 0. This single dose regimen was increased to 2.84 mg/kg and administered on Day -5, -3 and 0 with patency successfully prevented on Days 0 (2 of 2 monkeys) and -3 (1 of 2 monkeys). The compound was tested at higher doses in subsequent experiments and a single dose of 5.68 mg/kg found to be fully protective when administered 3 days prior to sporozoite challenge. TQ prevented patency in 2 of 2 animals at 1.78 mg/kg/day, 2 of 2 animals at 1.0 mg/kg/day, 7 of 7 animals at 0.316 mg/kg/day, 1 of 7 animals at 0.10 mg/kg/day, and none of 4 animals at 0.0316 mg/kg/day. TQ exhibits causal prophylactic activity with a calculated ED_{50} of 0.124 mg/kg/day x three days. This represents activity 10.5 times as potent as PQ against pre-erythrocytic stages.
Infected with sporozoites (Radical cure)	
P. cynomolgi bastianelli (Study report no. 2016N298130_00)	Rhesus monkeys (*Macaca mulatta*) were infected with 10^6 sporozoites. A rapidly rising parasitemia developed after a 7-9 day prepatent period. TQ in combination with CQ were administered for 7 days, by nasogastric intubation, when the rising parasite count exceeded $5000/mm^3$ (typically Days 10-12). Blood smears were prepared daily through Day 20 and every 2 days thereafter. If there was no relapse within 20 days of the initial clearance of parasitemia, parasitemia was followed for an additional 80 days. If there was no relapse within this period, the experiment was terminated and the monkey was considered "cured". The results show that tissue schizonticidal cures were achieved at dosages of 0.1, 0.316 and 1.0 mg/kg/day for 7 consecutive days by oral administration in combination with a completely suppressive blood schizonticidal regimen of CQ. WR 238605 was an effective agent against the persistent tissue stages of the parasite with a calculated CD_{50} of 0.172 mg/kg/day x 7 days. WR 238605 was 7.4 times more active than PQ as a tissue schizonticide. PQ diphosphate cured 90% of monkeys in this test system when administered at a dose of 1.3 mg/kg per day for 7 days (1.0 mg/kg free base) in combination with CQ.
P. cynomolgi /	Rhesus monkeys were infected IV with $0.9x10^6$ – $3.3x10^6$ sporozoites. Administration of the test

***Plasmodium* species/ strain (Reference)**	**Study summary**
NS (Study report no. 2016148_00)	drug was initiated the day after the initial parasitemia reached 5000/mm^3.for 7 days. Parasitemia was determined in each monkey by blood smears, two times prior to inoculation, daily from Day 6 post-inoculation until 20 days after the last dose administered, then twice weekly until negative parasitemia was found for 100 days post treatment. During relapses or recrudescences of parasitemia, blood smears were prepared daily. Monkeys in which parasitemia was cleared by the drug, but then reappeared, were treated with CQ phosphate, orally, at a dose of 10 mg/kg for 7 days whether or not CQ was included in the original regimen. Any monkey that developed parasitemia after the CQ treatment were considered relapses and terminated from the study. The number of monkeys in each group were small (n=2). The results show that tissue elimination of the malarial parasite occurred in some of the monkeys treated with a single dose of ≥3.5 mg/kg TQ. Treatment with a single 1.75 mg/kg dose of TQ in combination with CQ for 7 days was 100% effective in eliminating both blood and tissue forms of the parasites.
P. cynomolgi bastianelli (Dow et al., 2011)	Rhesus monkeys (*Macaca mulatta*) were infected with 10^6 sporozoites of *P. cynomolgi bastianelli* and blood smears prepared daily between Days 6 and 21 post-inoculation to measure parasitemia. Patency was consistently observed in all animals on Day 8. Oral treatment (intra-gastric feeding tube) with TQ was initiated for 1 – 3 days, once parasitemia of 5000/µL blood was reached. After study Day 21, if blood smears remained negative, they were monitored 3 days/week for 4 weeks and then twice weekly until 100 days post treatment, after which the animals were considered to be radically cured i.e., elimination of both blood and liver stages. The results show that TQ alone at a dose of 6 mg/kg/day for 3 days was effective in conferring radical cure. However, lower doses of TQ in combination with CQ were effective in conferring radical cure. Lower doses of TQ were not effective in suppressing parasitemia. CQ decreased parasite clearance time to 3 days when co-administered with TQ at 2 mg/kg/day for three days. At lower doses of TQ, CQ administered after initial TQ failure eventually resulted in radical cure. These data suggest that CQ compensates for the poorer blood schizonticidal effects of lower TQ doses. Anti-relapse activity of the minimum curative dose of TQ alone and in combination with CQ was determined. For this, 6 monkeys were administered TQ (0.6 mg/kg/day × 3 days) alone or in combination with CQ (24 mg/kg/day × 3 days) after a 10-day course of IM quinine to eliminate blood stage parasites (loading dose of 40 mg/kg base and followed by 20 mg/kg twice daily for 10 days; total dose 420 mg/kg) shown in pilot studies to eliminate blood stage parasites. All monkeys were negative by blood smear at the time of TQ and TQ/CQ dosing. The primary endpoint of the study was the proportion of radical cures observed in each group. The results show that radical cures were achieved in 6 of 6 monkeys administered TQ alone (0.6 mg/kg/day for three days) and 6 of 6 monkeys given TQ at the same dose combined with CQ (24 mg/kg/day for three days) following quinine treatment. Thus, the efficacy of anti-relapse activity of 1.8 mg/kg TQ is not dependent on co-administration with CQ.
NS-Not specified; IM=intramuscular	

References (Publications and Study Reports):

Cooper RD, Milhous WK, and Rieckmann KH. 1994, The efficacy of WR238605 against the blood stages of a CQ resistant strain of *Plasmodium vivax.* Trans Roy Soc Trop Med Hyg 88: 691-692.

DiTusa C, Kozar MP, Pybus B, Sousa J, Berman J, Gettayacamin M, Im-erbsin R, Tungtaeng A, and Ohrt C. 2014, Causal prophylactic efficacy of PQ, TQ, and atovaquone-proguanil against *Plasmodium cynomolgi* in a rhesus monkey model. *J Parasitol* 100 (5): 671-673.

Dow GS, Gettayacamin M, Hansukkjariya P, Imerbsin R, Kamcharoen S, Sattabongkot J, Kyle D, Milhous W, Cozens S, Kenworthy D, Miller A, Veazey J, and Ohrt C. 2011, Radical curative efficacy of TQ combination regimens in *Plasm0odium cynomolgi* infected Rhesus monkeys (*Macaca mulatta*). Malaria J 10: 212 (https://malariajournal.biomedcentral.com/articles/10.1186/1475-2875-10-212).

Milhous WK, Theoharides AD, Schuster BG, Puri SK, Dutta GP, Heisey GB, Kyle DE, Oduola AMJ, Dhar MM, Heiffer MH, Reid WA, and Davidson DE, Jr. New alternatives to PQ. FrS-12 New possibilities in the development of malaria drugs (1998) FrS-12-4.

Obaldia N III, Rossan RN, Cooper RD, Kyle DE, Nuzum EO, Rieckmann KH, and Shanks GD. 1997, WR 238605, CQ, and their combinations as blood schizonticides against a CQ-resistant strain of *Plasmodium vivax* in *Aotus* monkeys. Am J Trop Med Hyg 56 (5): 508-510.

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

Study report no. 2016N298150_00 (DAMD 17-82-C-2186) Report (US Army Medical Research and Development Command Contract No.); DAMD 17-83-C-3232. Drug evaluation in th (b) (4)

Study report no. 2016N298122_00 (DAMD17-18-G-9515)- (b) (4) Causal prophylactic testing in rhesus monkeys.

Study report no. 2016N298130_00 Report - (b) (4) January 31, 1987, Radical Curative Test in Rhesus Monkeys.

Study report no. 2016N298148_00 (SGRD-UWQ-J) Report – Col D E Davidson, Jr., VC March 1, 1988, Comparative study of WR238605 and PQ in the *Plasmodium cynomolgi* – Rhesus monkey curative test model.

15.5.2.Parasitological assessments

The parasitological assessments performed in the clinical trials included identification of *Plasmodium* species, quantitation of the asexual and gametocyte stage of the parasite using Giemsa stained thick and/or thin blood smears**.** Four slides (two thick films and one thin film, plus an additional unstained slide with both thick and thin films for contingency) were prepared at each time point for asexual and gametocyte count. Two slides were read by at least 2 trained microscopists at the site laboratory. The unstained contingency slide was shipped to the central laboratory, (b) (4) within a specified time, after preparation.

A. Parasitological evaluations at site laboratories:

At the site laboratory, the two thick film slides were processed, within 24 hours in a blinded manner, for determining the presence/absence of asexual and gametocyte forms of the parasites by two trained/qualified microscopists. If parasites were observed, both asexual and gametocyte forms of the parasites as well as WBC counts were performed simultaneously. The parasites were counted in different fields up to a total of 200 white blood cells (WBCs); if the number of asexual parasites was <10 after counting of 200 WBC, parasite counting was continued for up to 500 WBCs.

If the number of parasites on a thick film exceeded 250 per 50 WBC (heavy infection (>50,000 parasites/µL), the thick film count was discontinued. The count was performed on thin film instead.

Thin blood smears were used for identification of *Plasmodium* species.

If there was a significant discrepancy between the readings by the two readers (i.e. species difference or >20% difference in asexual parasite count or presence/absence of gametocytes) then the slides were read by a third independent reader (reader 3). The result from reader 1 or 2 that was closer to or which agreed with the third independent reading was regarded as the final result. The average of the two readings was recorded in the final report to the site Principle Investigator (PI) or Laboratory Director. The calculated parasite density (asexual and gametocyte count/µL) was recorded into the eCRF for each time point.

Slides were considered negative after review of 100 high-power fields and no parasites observed.

B. External quality assurance:

The unstained contingency slide of each time point was shipped to (b) (4) for further processing and archiving, on a weekly basis during the first three months of the study, then monthly thereafter only if good quality performance was shown in the weekly results.

A proportion of slides from each study site were examined in a blinded manner. The results were sent to the Applicant and the PI on a regular basis. If any of the slide QA results show less

than acceptable performance, then retraining discussions were conducted for corrective actions.

C. Parasite density:

The parasite density was calculated at each visit.

For thick film: Parasite density was based on patients' WBC count and was calculated as follows:

Parasites/µl= # Parasites counted x WBC count / # WBCs examined

For thin film: It was assumed that there are 250 RBCs per HPF (RBC count from 8 HPF equal 2000 RBC); 4,000,000 RBCs/µL blood was used to calculate parasite density.

Parasite/µL = (# of parasites in 8 HPF /2000) x4,000,000

16 Division Director (OCP)

Concur with the review.

17 Division Director (OB)

Concur with the review.

18 Division Director (Clinical)

Concur with review.

19 Office Director (OAP)

Concur with review.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GREGORY F DIBERNARDO
07/20/2018

EDWARD M COX
07/20/2018

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	May 15, 2018
To:	Elizabeth O'Shaughnessy, MD, OAP/DAIP
From:	Jennifer Lan, Medical Officer, DPARP
Through:	Miya Paterniti, Medical Team Leader, DPARP
Through:	Banu Karimi-Shah, Acting Deputy Director, DPARP
Subject:	Possible anaphylaxis with Krintafel (tafenoquine)

General Information

NDA/IND#:	NDA 210795
Sponsor:	GlaxoSmithKline
Drug Product:	Krintafel (tafenoquine)
Request From:	Gregory DiBernardo, Regulatory Project Manager, OAP/DAIP
Date of Request:	April 16, 2018
Date Received:	April 30, 2018
Materials Reviewed:	Clinical Study Report for Study TAFF114582 included in Original NDA submission dated November 22, 2017 (SD 1, eCTD 0000)

I. Executive Summary

This is a Medical Officer response to the request for consultation from the Office of Antimicrobial Products/Division of Anti-Infective Products (OAP/DAI), regarding two serious adverse events (SAEs) of hypersensitivity-related reactions. OAP/DAI is requesting DPARP's input regarding whether these two cases represent drug-induced hypersensitivity and whether they constitute cases of anaphylaxis. Furthermore, they seek recommendations as to whether labeling changes are needed to section 5.4.

After review of the two case narratives, we do not believe the two cases are consistent with anaphylaxis. In both cases, the symptoms started weeks after ingesting the investigational drug. Furthermore, the long duration of symptoms is not consistent with anaphylaxis. We do not expect the long-half life (14-19 days) of tafenoquine to alter the initiation time or duration of anaphylaxis; however, it may contribute to prolonged duration of hypersensitivity symptoms. The first case report is likely secondary to the reported preceding viral illness, but a drug-induced hypersensitivity reaction cannot be excluded. The second case narrative may represent a delayed hypersensitivity reaction given the severity of symptoms with no alternative explanation reported. As such, we agree that inclusion of hypersensitivity reactions in the Warnings and Precautions section of the label is warranted.

II. Brief Overview of Drug

Tafenoquine (TQ) is an 8-aminoquinoline antimalarial drug that is under development as a 300 mg single-dose [redacted (b) (4)] The half-life of tafenoquine is [redacted (b) (4)] days. Other antimalarial drugs in the aminoquinoline class include primaquine (8-aminoquinoline) and mefloquine (4-aminoquinoline). Per the prescribing information (mefloquine revised 5/2016, primaquine revised 1/2018) hypersensitivity reactions have been reported with mefloquine use, but not with primaquine. Tafenoquine is proposed to have an advantage over the currently available therapies as it is proposed as a single dose, compared to primaquine which is dosed over 14 days.

The two case narratives originate from a randomized, single-blind, placebo-controlled, parallel group study investigating the changes in QT duration due to therapeutic and supratherapeutic doses of TQ compared to placebo and moxifloxacin in healthy subjects. To evaluate the concentration-response relationship, a supratherapuetic TQ dose of 1200 mg was selected. This dose was administered as 400 mg daily for three consecutive days. In addition to this, two additional doses of TQ were also used in this study; the 300 mg single dose and the 600 mg single dose, both administered on Day 3. These subjects received placebo on Days 1 and 2. Another dose group received placebo on Days 1 and 2 and 400 mg moxifloxacin on Day 3. The dose selection was primarily based on the adverse event profile of TQ as well as the goal to achieve exposure that was multiples of anticipated maximal therapeutic exposure. Two hundred fifty-one subjects completed the study as planned. Five subjects were lost to follow-up. Two subjects withdrew consent to participate in the study, and one subject was withdrawn due to an adverse event. Tafenoquine's clinical development program included 4,129 subjects. It is notable that none of the other clinical studies reported a hypersensitivity SAE.

II. Review of Cases

A. Case #1

A 23-year-old female reported that she developed swelling of the throat and diffuse hives 17 days after the start of the investigational product and 15 days after the last dose. She received placebo on Days 1 and 2, and TQ 600 mg and placebo on Day 3. She presented to the emergency room and received diphenhydramine and steroids and was discharged with six days of oral steroids. The hives reportedly waxed and waned over the next four days despite being on steroids. Concurrent with the hives, the participant reported some angioedema of the hands and feet. This event was proceeded by a viral upper respiratory infection two weeks beforehand. The participant denies any new foods, NSAID use, or recent stings.

Reviewer Comments: *Based on the delayed onset of symptoms (15 days) and the lack of respiratory compromise, reduced blood pressure or associated symptoms of end-organ dysfunction, this case, does not meet the NIAID/FAAN criterion #1 for anaphylaxis (Table 1). The duration of symptoms is also inconsistent with anaphylaxis. The patient reported intermittent symptoms lasting 4 days. Anaphylaxis symptoms usually last only for a few hours. Given her proceeding viral illness, her multi-day intermittent hives*

and angioedema were likely viral-induced; however we cannot exclude a drug induced hypersensitivity.

B. Case #2

A 45-year-old female with a history of asthma, reported that 13 days after receiving the last dose of the investigational product, she developed hives. The subject received placebo on Days 1 and 2, and TQ 300 mg and placebo on Day 3. She went to the emergency department twice for the hives and was treated with prednisone, diphenhydramine, and an H2 blocker. She reports that symptoms worsened and around 16 days after receiving the investigational product, symptoms progressed to shortness of breath, lip swelling, and worsening of the hives. She was given an albuterol nebulizer treatment and observed for 8 hours in the emergency department and sent home. Vitals were stable. Per documentation, symptoms resolved approximately 8 days after initial onset. The subject denies any previous history of allergies or any new exposures during that time.

Reviewer Comments: This case also does not meet the criteria for anaphylaxis given the delayed onset of symptoms (13 days). The duration of symptoms was also inconsistent with anaphylaxis. Given the lack of any other clear trigger, it is possible that this represents a hypersensitivity reaction to TQ and that the prolonged symptom duration (8 days) may be due to the long-half-life of TQ (14-19 days).

Table 1. Clinical criteria for diagnosing anaphylaxis[1]

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

III. Label

Though we do not believe the above cases meet criteria for anaphylaxis, case 1 possibly represents a TQ-induced hypersensitivity reaction and case #2 may represent a case of TQ induced hypersensitivity. As such, we agree that inclusion of hypersensitivity reactions in the Warnings and Precautions Section of the label is warranted. Our proposed edits are shown below:

Highlights

4. Contraindications

- Patients with known ~~serious~~ hypersensitivity ~~reactions (e.g., angioedema)~~ to tafenoquine, other 8-aminoquinolines, or any ~~component~~ of the ingredients ~~formulation~~ of KRINTAFEL. (*see Warnings and Precautions 5*.4)

5.4 Hypersensitivity Reactions

Serious hypersensitivity reactions (e.g., urticaria, angioedema, (b) (4)) have been observed in with administration of KRINTAFEL *[see Adverse Reactions (6.1)]*. Institute appropriate therapy if hypersensitivity reactions occur. Do not re-administer KRINTAFEL to patients who develop hypersensitivity to KRINTAFEL.

(b) (4)

VII. References

1. Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy 1988; 18:515.

2. Sampson, H., Muñoz-Furlong, A., Campbell, R., Adkinson, N., Bock, S., Branum, A., Brown, S., Camargo, C., Cydulka, R., Galli, S., Gidudu, J., Gruchalla, R., Harlor, A., Hepner, D., Lewis, L., Lieberman, P., Metcalfe, D., O'Connor, R., Muraro, A., Rudman, A., Schmitt, C., Scherrer, D., Simons, F., Thomas, S., Wood, J., & Decker, W. (2006). "Second symposium on the definition and management of anaphylaxis: Summary Report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium." J Allergy Clin Immunol. 117:391-397.

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/s/

JENNIFER P LAN
05/15/2018

MIYA O PATERNITI
05/15/2018

BANU A KARIMI SHAH
05/15/2018

Medical Officer's Consult Review of NDA 210795
Ophthalmology

NDA 210795	Submitted date:	November 22, 2018
	Consult Request:	November 22, 2018
	Review completed:	May 7, 2018

Product Name: **Krintafel (tafenoquine) tablets, for oral use**

Applicant: **GlaxoSmithKline Intellectual Property Development Ltd. England**

Cross Referenced IND: **101471**

Consult Request:

Tafenoquine is a novel 8-aminoquinoline anti-malarial drug being co-developed by GSK and the Medicines for Malaria Venture (MMV). TQ has activity against the liver hypnozoite *P. vivax* parasite and an approximate 15-day half-life that allows treatment of the liver hypnozoite parasite in *P. vivax* malaria with a single oral dose. The proposed indication for tafenoquine is for the radical cure (prevention of relapse) of *P. vivax* malaria in adults and adolescents ≥16 years of age. The recommended dose is a single 300 mg dose (2 x 150 mg tablets) taken in conjunction with chloroquine (b) (4)

EDR Link to New NDA 210795: \\CDSESUB1\evsprod\NDA210795\0000

1. The Division of Anti-Infective Products requests your review and comments on the ophthalmic safety of tafenoquine which was studied in Study 201807, a phase 1, multi-center, single-masked, randomized, placebo-controlled, parallel group study to investigate the ophthalmologic safety and pharmacodynamics of 300mg single doses of tafenoquine (SB-252263) in adult healthy volunteers.

The interim study report for Study 201807 can be located at \\CDSESUB1\evsprod\NDA210795\0000\m5\53-clin-studrep\535-rep-effic-safety-stud\p-vivax-malaria\5354-other-stud-rep\201807

The datasets for Study 201807 can be located at \\CDSESUB1\evsprod\NDA210795\0000\m5\datasets\201807

2. We ask your comments on the ophthalmic safety of tafenoquine as described in section 2.1.5.3 (sic) in the Summary of Clinical Safety which can be located at \\CDSESUB1\evsprod\NDA210795\0000\m2\27-clin-sum

3. Please provide labeling recommendations based on your review of the ophthalmology data. A draft label can be located at \\CDSESUB1\evsprod\NDA210795\0000\m1\us\114-labeling

Reviewer's Comment: *Comments in this review are limited to areas of ophthalmologic concern.*

NDA Organization

Module 1.14 contains proposed product labeling.
Module 2.7.4 contains the Summary of Clinical Safety.
Module 5.3.5.4 contains the study report for 210807: A Phase 1, Multi-center, Single-masked, Randomized, Placebo controlled, Parallel-group Study to Investigate the Ophthalmologic Safety and Pharmacodynamics of 300mg Single Doses of Tafenoquine (SB-252263) in Adult Healthy Volunteers.

Background

Primaquine (PQ; an 8-aminoquinoline) is an approved drug for the radical cure (relapse prevention) of *Plasmodium vivax* (*P. vivax*) malaria. It decreases relapse by eradicating the reservoir of dormant *P. vivax* hypnozoites in the liver. While efficacious against *P. vivax*, the 7 to 14-day treatment regimen for PQ can lead to reduced compliance and hence reduced effectiveness. Tafenoquine (TQ) is being developed as a potential single dose radical cure (relapse prevention) of *P. vivax* malaria. In common with cationic amphiphilic drugs, TQ has the potential to cause phospholipid accumulation in the cornea seen clinically with a slit lamp as a vortex keratopathy.

Ophthalmic assessments were included in several early clinical studies of TQ. While such investigations were primarily intended to evaluate the risk for corneal effects, retinal findings were also reported. However, there was no clear pattern of pathology and there was uncertainty as to etiology and the timeline of the findings (e.g., given a lack of baseline retinal photography).

This study *(Study 201807)* was conducted to provide sufficient evidence of retinal safety to support the use of TQ as a potential single dose radical cure treatment for patients with P. vivax malaria (i.e., co-administration of a schizonticidal drug with TQ). Based on the currently accumulated TQ retinal safety evidence and published literature regarding the screening for chloroquine and hydroxychloroquine retinopathy, this clinical trial was conducted to assess retinal changes from baseline using spectral domain optical coherence tomography (SD-OCT) and fundus auto fluorescence (FAF) at month 3 (90 days) post-dose in adult healthy subjects and a few additional assessments including best corrected distance visual acuity and slit lamp evaluations of the eyes.

Reviewer's Comment:

Reference is made to the January 25, 2015, meeting between the applicant and the FDA to discuss the ophthalmic safety study design.

GSK stated that they and the Medicines for Malaria Venture (MMV) were proposing 100 subjects to be evaluated in the NDA and if an abnormality/signal was seen then more subjects would be added. FDA stated that a 3-month study with 100 patients would only rule out Adverse Events (AEs) at an approximately 3% level; FDA requested assurance at an approximately 1% AE level and to do this, GSK would need a 300-subject study.

FDA agreed to accept a subset of 100 subjects at the time of NDA submission and 200 additional subjects after application submission. This would include a baseline evaluation and a follow-up (3-month evaluation) for all 300 patients. The FDA expected to see the following tests evaluated at both baseline and follow-up: OCT, autofluorescence, slit lamp, and visual acuity tests.

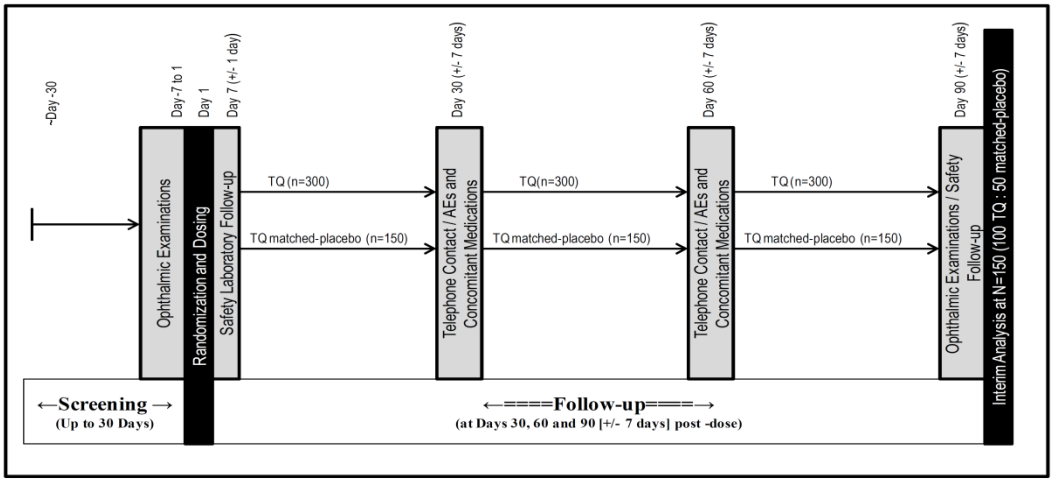
GSK inquired why FDA was concerned with a 3-month evaluation for a single dose drug therapy and not considering a 28-day evaluation. FDA responded that retinal changes are sometimes transient and the Agency was more concerned with persistent abnormalities.

GSK inquired if they could propose a descriptive study without a control arm or if FDA thought a control was needed. FDA stated that retinal abnormalities had already been seen in previous studies. If GSK moved forward with their new study without a control arm, it would be impossible to differentiate an abnormality caused by the drug versus background abnormalities. FDA suggested a control arm in their new study (Study 201807), which could include a 2:1 randomization schedule.

Study 201807

This was a multi-center, randomized, single-masked placebo-controlled, parallel-group study of a 300-mg single oral dose of TQ in healthy adult subjects. The study duration, including screening and follow-up, was not expected to exceed beyond the 30-day screening period and the Day 90 (-7 days to +14 days) study visit for any subject in the study (Figure 1).

Figure 1 Study Design Schematic



Source: Module 5.3.5.4

Eligible subjects were randomized in a 2:1 ratio, 300 mg TQ or matched placebo in the study to have ≥300 subjects treated with TQ. A total of 500 subjects were randomized to ensure an adequate number of subjects were evaluable for the primary endpoint. An interim analysis was conducted once approximately 100 TQ and 50 placebo subjects had completed baseline and Day 90 follow-up assessments. Study subjects received TQ as a single oral dose (with food). Subjects who had provided written informed consent were randomized to treatment within 30 days of screening. Following the initial screening assessments, eligible subjects underwent baseline ophthalmic examinations and were randomized to treatment (TQ or matched-placebo) within 7 days of ophthalmic screening examinations. Subjects returned to the clinic for safety laboratory collections and vital signs on Day 7 (±1 day) and received Day 30 and Day 60 (±7 days) post-dose safety contacts (telephone calls or face-to-face contact at the Investigator's discretion) from the

site. Subjects then returned for a follow up ophthalmic examination visit at approximately 90 days (-7 days to +14 days) post-dose. Pharmacodynamic assessments included key SD-OCT measurements of central retinal thickness and appearance of the retina on FAF at the screening and Day 90 follow-up visits. Visual acuity using Early Treatment Diabetic Retinopathy Study (ETDRS) chart reading was also measured. Additional retinal morphology was assessed by SD-OCT, and fundus photography captured at the screening and Day 90 visits.

Assessments of central retinal thickness, central subfield thickness, total macular volume and ellipsoid zone disruption determined from SD-OCT as well as the retinal appearance on FAF were used for primary analyses. Other ophthalmic assessments including BCVA, slit lamp, and fundus photography were also conducted. The assessments were done at screening/baseline and at Day 90 (-7 days to +14 days) follow-up visits. Refer to the Time and Events Table (Table 33) for assessments performed during the course of the study.

Safety was assessed by complete ophthalmic examinations, vital signs assessments, AE reporting and a single laboratory safety assessment performed on Day 7 (±1 day). There was no formal independent data monitoring committee for this study; however, a third-party central review center performed independent assessments of all imaging studies in the trial for the purpose of providing ocular safety data. The readers were masked to study treatment.

Table 33 Time and Events Table

Procedures	Screening	Baseline		Safety Follow-ups			Notes
	Day -30 to 1	Day -1	Day 1	Day 7	Days 30 & 60	Day 90	*Visit Window: ± 1 day for Day 7 Visit;* *Visit Window: ± 7 days for Day 30, 60, and 90 Visits* *Overnight stay at the unit from Day -1 to Day 1 is not mandatory.*
Informed Consent	X						
Demographics	X						
Assess Eligibility Criteria	X						
Medical/Ophthalmic History	X						
Medication History	X						
Safety Assessments							
Brief Physical Examination and Weight	X						
ECG and Vital Signs	Triplicate			X			• *Assessments may be repeated prior to dosing at discretion of the investigator*
Drug/Alcohol/Cotinine testing	X	X				X	• *Pregnancy (♀ of childbearing potential only)/Drug/Alcohol testing performed according to site standard. Results will be received and confirmed as negative prior to dosing.*
Clinical Labs	X			X			• *Only single Vital Signs at Day 7.*
Pregnancy Test	X	X				X	
Telephone contact					X		*Safety follow-up for events captured by telephone is at the Investigator's discretion. If required, the Investigator may elect to replace telephone contact with a face to face visit.*
Concomitant Treatments		←==========X==========→					
Adverse Events (AEs)		←==========X==========→					
Ophthalmology Assessments							• *Screening Ophthalmology Assessments to be performed within 7 days of randomization.* • *Assessment to be performed at retinal center/specialist.* • *Subjects must meet all safety criteria before ophthalmic assessments.*
Contact Reading Center	X					X	*Prior to conducting ophthalmic assessments, contact reading center to inform of incoming data for confirmation of acceptability.*
Refraction +ETDRS BCVA	X					X	
Slit lamp - Anterior and Posterior Segment Evaluation	X					X	
IOP	X					X	
Fundus Photography	X					X	
Auto-florescence Imaging	X					X	

Procedures	Screening	Baseline		Safety Follow-ups			Notes
	Day -30 to 1	Day -1	Day 1	Day 7	Days 30 & 60	Day 90	*Visit Window: ± 1 day for Day 7 Visit;* *Visit Window: ± 7 days for Day 30, 60, and 90 Visits* *Overnight stay at the unit from Day -1 to Day 1 is not mandatory.*
SD-OCT	X					X	
Randomization			X				• Subjects will not be randomized until completion of pre-dose ophthalmic assessments.
Study drug/placebo and meal			X				• Dosing must occur within 7 days of completion of pre-dose ophthalmic assessments. • Observe subjects inpatient for 4 hours after dosing (see also Section 6.1 of protocol).

Inclusion Criteria
Key inclusion criteria: Male or female subjects between 18 and 45 years of age inclusive, with a body weight ≥35 kg and ≤100 kg, healthy as determined by the investigator or medically qualified designee, with hematology and chemistry values within the normal range, capable of giving signed informed consent. Subjects of non-reproductive potential or capable of adhering to contraceptive requirements.

Exclusion Criteria
Key exclusion criteria:

- Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
- Use of prescription (except female contraception and acetaminophen [paracetamol] at doses of ≤2 g/day) or non-prescription drugs.
- History of sensitivity to TQ, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicated their participation.
- A BCVA (bilateral) at screening of ≤72 letters. Eye disease that could compromise assessment of BCVA or imaging of the posterior pole by fundus photography, or SD-OCT, FAF, or is likely to require intervention during the ~4-month study participation (e.g. cataract, glaucoma with documented visual field loss, ischemic optic neuropathy, retinitis pigmentosa).
- History of retinal vascular disease, retinal detachment, inflammatory disease, central serous chorioretinopathy, or other retinal disease that may affect posterior retinal function or architecture.
- Vitreo-retinal interface disorders (e.g. epiretinal membrane, vitreo-macular traction) that may affect posterior retinal function or architecture, intraocular surgery within 3 months of dosing, laser photocoagulation within 3 months of dosing, high myopia (defined as equal to or worse than -6.00 diopters), anterior, intermediate or posterior uveitis (active or history of) or history of significant intraocular infectious disease (e.g., conjunctivitis is not acceptable to include) or another active inflammatory disease.
- An SD-OCT central subfield thickness <250 microns or >290 microns (Note: A central subfield thickness outside this range will be evaluated by the central reading center and, if all other factors on the scan are considered normal, the subject may be considered eligible at the discretion of the central reading center).
- Presence of significant abnormal patterns on FAF or ocular abnormalities on fundus photography at screening.
- Uncontrolled intraocular pressure greater than 22 mmHg.
- Documented phenotypic Glucose-6-phosphate dehydrogenase (G6PD) deficiency, determined by a quantitative assay of enzyme activity. Defined as <70% of locally defined median.

Investigational Products
Subjects were assigned to TQ or matched-placebo (2:1) in accordance with the randomization schedules generated by Clinical Statistics, prior to the start of the study, using validated internal software. Subjects in the TQ group were administered 2 tablets of TQ 150 mg orally and subjects in the placebo group were administered 2 tablets of placebo orally.

Ophthalmic Examinations
The independent reading center reviewed the baseline data in a masked fashion to confirm eligibility. They recommended to the site investigator and/or ophthalmologist whether or not to screen fail/exclude a subject from the study based upon their review.

Baseline and Day 90 ophthalmic examinations were performed by the same Investigator (e.g., technician and Ophthalmologist/Retinal Specialist) using the same equipment (e.g., SD- OCT).

Refraction and Visual Acuity: Refraction BCVA measured using ETDRS visual acuity charts at defined study visits by an examiner that had been appropriately trained.

General Ophthalmic Examination: A complete eye exam was planned to be performed and included pupil, motility and confrontation visual field examination; slit lamp evaluation of anterior ocular structures (including cornea); intraocular pressure (IOP) measurement; dilated Fundus Examination (Indirect ophthalmoscopy and slit lamp biomicroscopy, including the lens). Optical Coherence Tomography (OCT): SD-OCT images/scans were obtained and collected at specified visits as per the central reading center OCT protocol handbook, by an appropriately trained photographer/technician using SD-OCT equipment that had been approved by the central reading center. These images were evaluated by an Investigator/sub-Investigator and confirmed by reading center for protocol inclusion/exclusion criteria and safety monitoring. Images were sent to and evaluated by the central reading center for pharmacodynamic effect.

Fundus Autofluorescence (FAF): An agreed protocol set of FAF images were obtained at specified visits as per the FAF protocol handbook provided by the central reading center. Images were evaluated by Investigator/sub-Investigator and confirmed by the central reading center for protocol inclusion/exclusion criteria and safety monitoring. These images were sent to, and evaluated by, the central reading center for pharmacodynamic effect assessment.

Fundus Photography (FP): Fundus photographs were obtained at screening and Day 90 follow-up visits as per the central reading center protocol handbook. Images were evaluated by Investigator/sub-Investigator and confirmed by the central reading center for protocol inclusion/exclusion criteria and safety monitoring. These images were sent to, and evaluated by, the central reading center for assessment.

Primary Analyses
The primary ophthalmic safety analyses were based on the primary ophthalmic safety population, unless otherwise specified. The primary endpoint was the proportion of subjects treated with TQ with significant protocol-defined retinal changes from baseline to Day 90 follow up visits. The point estimate and the corresponding 95% confidence interval (CI) for the proportion were provided. The outcome was determined from key parameters from SD-OCT scans and FAF images. For the primary endpoint, a subject was considered to have a clinically significant retinal change if any of the five parameters listed below (Table 3) indicated a change from baseline in either eye.

Table 3 Primary Endpoint – Parameters to Define Defining a Retinal Finding

Parameter	Result (Change from baseline)	Comments
OCT Central Subfield Thickness	Yes/No	Yes if change from baseline of at least 40 microns
OCT Total Macular Volume	Yes/No	Yes if change from baseline of at least 10%
OCT Central Retinal Lesion Thickness[a]	Yes/No	Yes if change from baseline of at least 40 microns (manual reading)
OCT Ellipsoid Zone Disruption	Yes/No	Yes if change from baseline width of at least 15%
Abnormal autofluorescence patterns	Yes/No	Yes if overall pattern = Normal at screening AND Abnormal at Day 90

a. Central Retinal Lesion Thickness (at central 1 mm of the center scan) is the distance between the inner limiting membrane of the retina and the inner border of the choriocapillaris (inclusive of subretinal or sub-RPE fluid collections and of the thickness of any observable choroidal neovascular membrane or scar tissue if present) measured in the central 1 mm of the center scan. If no abnormal lesion noted, the central retinal lesion thickness represents the central retinal thickness at the center point of the macula.

Source: Module 5.3.5.4

Reviewer's Comment:

On January 25, 2018, the Agency requested the following be submitted to the NDA:

- *Request 1a: OCT protocol handbook and 1b: FAF protocol handbook*
- *Request 2: CRFs for discontinued subjects*
- *Request 3: 10% sample of source images as JPEG files organized by site, then Subject, then image type/eye and then by visit day (Baseline and Day 90)*
    - *As agreed the images would be from an ~ 10% sample of the interim subject dataset (164 subjects) and will be the images from 17 subjects (6 placebo and 11 TQ 300mg subjects).*

Subject Disposition

A total of 1522 subjects were screened for the study. The main reason for screening failure was not meeting inclusion/exclusion criteria (915/1022 screen failures).

Table 1.3
Summary of Reasons for Screen Failure

	Total (N=1522)
Screening Status	
ENROLLED	500 (33%)
FAILED	1022 (67%)
Reason for failure [1]	
DID NOT MEET INCLUSION/EXCLUSION CRITERIA	915 (60%)
STUDY TERMINATED BY SPONSOR	3 (<1%)
LOST TO FOLLOW-UP	21 (1%)
PHYSICIAN DECISION	43 (3%)
WITHDRAWAL BY SUBJECT	45 (3%)

Source: Module 5.3.5.4

A total of 500 subjects were enrolled, of which 498 subjects were treated and ≥97% of subjects in the placebo and TQ groups completed the study (Table 4). Two TQ subjects were not able to swallow study treatment, were withdrawn from the study, and were excluded from the Safety Population. Enrollment by treatment group was balanced across the 3 study centers.

Table 4 Subject Disposition (Safety Population)

	Placebo N=168	TQ 300 mg N=330	Total N=498
Completion status, n (%)			
Completed	165 (98)	321 (97)	486 (98)
Withdrawn	3 (2)	9 (3)	12 (2)
Reason for withdrawal, n (%)			
Lost to follow-up	2 (1)	6 (2)	8 (2)
Withdrawal by subject	1 (<1)	3 (<1)	4 (<1)

Source Data: Table 1.1

Source: Module 5.3.5.4

Populations Analyzed

- The **Safety Population** consisted of all subjects who received at least one dose of study treatment.
- The **Primary Ophthalmic Safety Population** included all subjects in the safety population who also had screening and Day 90 OCT and FAF measurements that allowed the primary endpoint to be determined.
- The **Expanded Ophthalmic Safety Population** included all subjects in the safety population who had screening and Day 90 OCT and FAF measurements that allow the primary endpoint to be determined after imputation of missing data.
- The **Per Protocol Ophthalmic Safety Population** included all subjects in the Primary Ophthalmic Safety Population who did not have an important protocol deviation that may have affected the primary endpoint.

Table 7 Populations analyzed

Population	Placebo, n(%)	TQ 300mg, n(%)	Total, n (%)
All subjects screened			1522
Randomised	168	332	500
Safety	168 (100)	330 (>99)[a]	498 (>99)
Primary ophthalmic safety	161 (96)	306 (92)	467 (93)
Per-protocol ophthalmic safety	152 (90)	294 (89)	446 (89)
Expanded ophthalmic safety	165 (98)	319 (96)	484 (97)

Source: Table 1.4

a. 2 enrolled TQ subjects did not swallow IP for treatment.

Source: Module 5.3.5.4

There were 21 subjects in the Primary Ophthalmic Population excluded from the Per Protocol Population, primarily due to use of an excluded medication.

Table 6 Protocol Deviations Leading to Exclusion from the Per Protocol Population (Primary Ophthalmic Safety Population)

Category/coded term	Placebo N=161	TQ 300 mg N=306	Total N=467
Any deviation	**9 (6)**	**12 (4)**	**21 (4)**
Eligibility criteria not met	0	2 (<1)	2 (<1)
Excluded medication, vaccine or device	9 (6)	9 (3)	18 (4)
Medication, excluded by the protocol, was administered	3 (2)	2 (<1)	5 (1)
Other excluded medication, vaccine or device deviation	6 (4)	7 (2)	13 (3)
Wrong study treatment/ administration/dose	0	2 (<1)	2 (<1)

Source Data: Table 1.10

Source: Module 5.3.5.4

Demographics

Demographic and baseline characteristics were balanced between the treatment groups.

Table 8 Demographic and Baseline Characteristics (Safety Population)

	Placebo N=168	TQ 300mg N=330	Total N=498
Age (years)			
Mean	30.0	29.0	29.4
SD	7.23	7.17	7.20
Median	29.0	28.0	28.0
Min.	17[a]	17[a]	17[a]
Max.	45	45	45
Sex, n (%)			
Male	70 (42)	136 (41)	206 (41)
Female	98 (58)	194 (59)	292 (59)
Ethnicity, n (%)			
Hispanic or Latino	24 (14)	65 (20)	89 (18)
Not Hispanic or Latino	144 (86)	265 (80)	409 (82)
Race detail, n (%)			
African American/African heritage	58 (35)	114 (35)	172 (35)
American Indian or Alaskan native	1 (<1)	2 (<1)	3 (<1)
Asian	7 (4)	16 (5)	23 (5)
Native Hawaiian or other Pacific islander	3 (2)	0	3 (<1)
White	92 (55)	187 (57)	279 (56)
Multiple	7 (4)	11 (3)	18 (4)
G6PD enzyme activity (IU/g Hb)			
Mean	10.47	10.69	10.62
SD	1.231	1.196	1.211
Median	10.40	10.70	10.60
Min	7.5	7.6	7.5
Max	15.3	16.1	16.1

Source: Table 1.6, Table 1.7

a. Subjects were not recorded as having protocol deviations for age because this was imputed age from a month-year format only. Real ages were confirmed ≥18.

Source: Module 5.3.5.4

Ophthalmic Safety Assessment Analysis Results – Primary Endpoint

The primary endpoint of the study was a composite of SD-OCT and FAF changes from baseline. As shown in the table below, 1 subject in each treatment group was described as having a change in the ellipsoid zone disruption (EZD). No subject in the study had a change in FAF.

	Placebo, N=168				TQ 300 mg, N=330			
Eye:	**Right**	**Left**	**Either**	**Both**	**Right**	**Left**	**Either**	**Both**
Central subfield thickness								
n	161	158	158	158	305	306	304	304
No, n (%)	161 (100)	158 (100)	158 (100)	158 (100)	305 (100)	306 (100)	304 (100)	304 (100)
Central retinal lesion thickness								
n	162	162	162	162	308	308	308	308
No, n (%)	162 (100)	162 (100)	162 (100)	162 (100)	308 (100)	308 (100)	308 (100)	308 (100)
Total macular volume								
n	162	162	162	162	308	308	308	308
No, n (%)	162 (100)	162 (100)	162 (100)	162 (100)	308 (100)	308 (100)	308 (100)	308 (100)
Ellipsoid zone disruption								
n	162	162	162	162	308	308	308	308
Yes	1 (<1)	0	1 (<1)	0	1 (<1)[a]	0	1 (<1)[a]	0
No, n (%)	161 (>99)	162 (100)	161 (>99)	162 (100)	307 (>99)	308 (100)	307 (>99)	308 (100)
Autofluorescence pattern								
n	161	161	161	161	306	306	306	306
No, n (%)	161 (100)	161 (100)	161 (100)	161 (100)	306 (100)	306 (100)	306 (100)	306 (100)

Source: Table 3.8

a. Subject had a baseline EZD and was enrolled in error. However, this protocol deviation was not captured in the study.

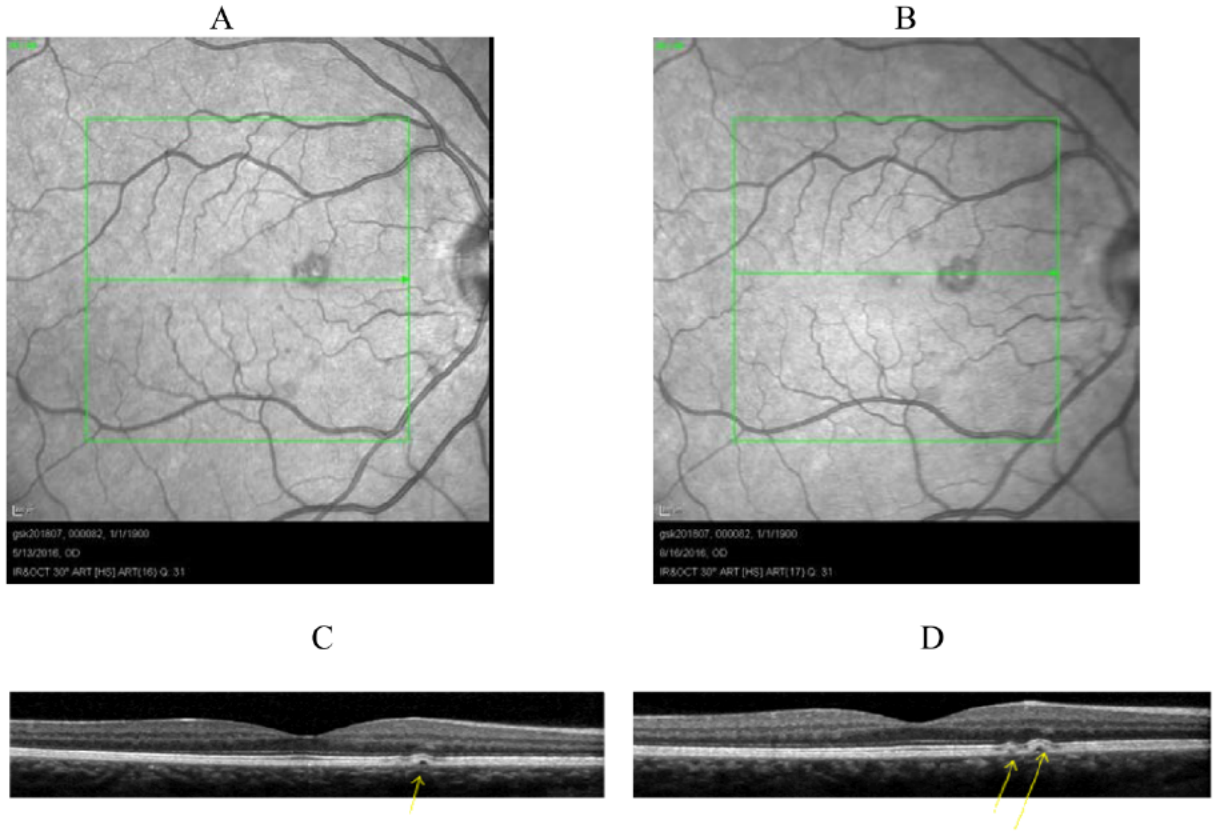
Source: Module 5.3.5.4

Brief descriptions are given for the 2 subjects who met the primary endpoint for direct comparison.

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

Subject (b) (6) had ellipsoid zone (EZD) disruption of >15% representing change from baseline in one (right) eye at the Day 90 follow up assessment. This subject had a baseline EZD width of 27.5 µm and was enrolled in error. The contralateral (left) eye did not meet this endpoint. None of the other 4 primary endpoints were met. Of note this subject reported no visual AEs and best corrected visual acuity did not change from baseline. Fundus examination and photography were unchanged from baseline.

Figure 4 SD-OCT for Subject (b) (6) (Baseline vs Day 90)



Note: Baseline scans are on the left; scans from the Day 90 assessment are on the right.

Source: Module 5.3.5.4

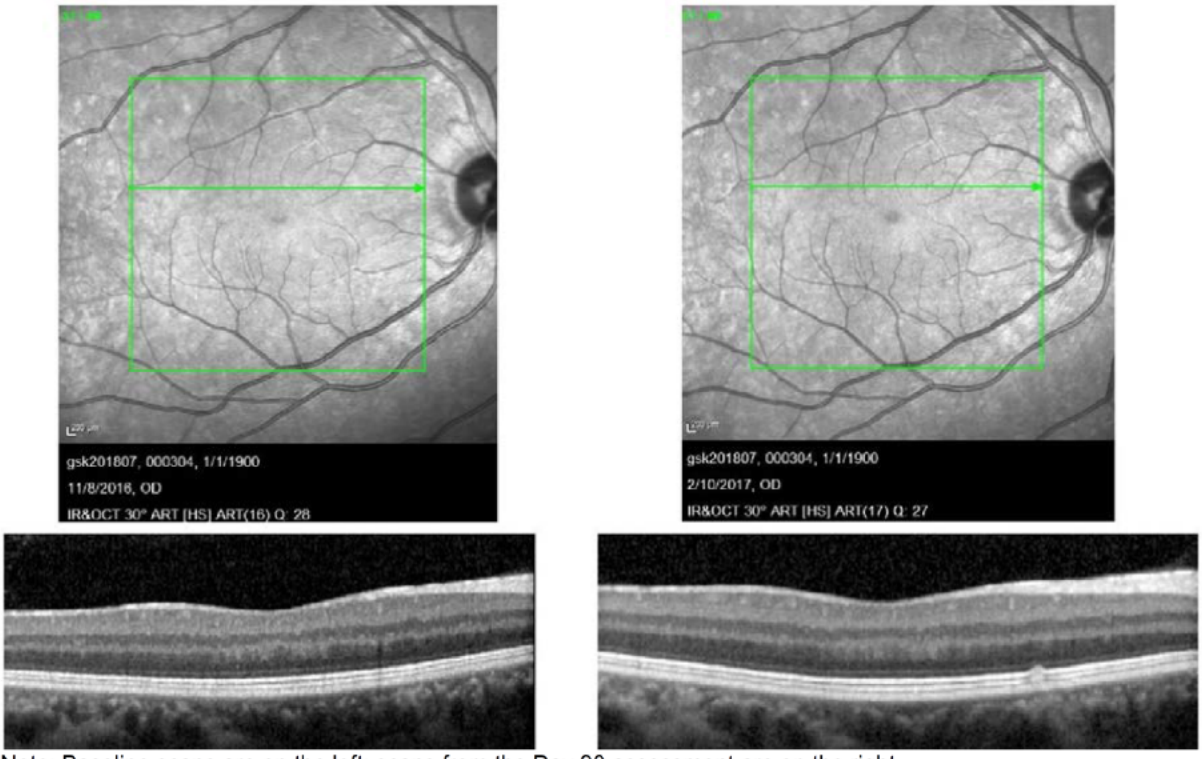
Reviewer's Comment:

As the ellipsoid zone disruption was present at baseline, this subject should have been a screen failure but was randomized to receive study drug (tafenoquine arm).

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

Subject (b) (6) had a unilateral EZD of >15% representing a change from baseline in the right eye, which was confirmed to be not due to scan misalignment. The subject did not have EZD at baseline, but had an EZD width of 128 µm at the Day 90 assessment. The contralateral (left) eye did not have a change from baseline.

Figure 5 Retinal Images from Subject (b) (6)



Note: Baseline scans are on the left; scans from the Day 90 assessment are on the right.

Source: Module 5.3.5.4

Serious Adverse Events/Deaths

There were no serious adverse events in the study. There were no deaths in the study.

Ophthalmic Adverse Events

The ophthalmological AEs were generally balanced between the treatment groups. Most AEs occurred in only 1 subject, or in 1 subject in each treatment group.

Subject (b) (6) in the TQ group had an AE of ocular icterus, coincident with AEs of dry eye and foreign body sensation in eyes. The laboratory results did not indicate significant hemolysis, as the subject's hemoglobin was 122 g/L at baseline and 124 g/L at Day 7, and hematocrit, both erythrocyte mean corpuscular hemoglobin and volume, and erythrocyte number, all increased

from baseline to the Day 7 assessment (Source: Listing 21). None of the other laboratory assessments for Subject (b) (6), including bilirubin, were of potential clinical importance.

Subject (b) (6) in the TQ group had an AE of corneal deposits which was diagnosed as an occurrence of Wesley's immune ring and not as vortex keratopathy.

Vortex keratopathy was reported in 1 subject (TQ group) at the Day 90 assessment. This was not reported as an AE. Specifically, 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. The report of vortex keratopathy was due to a data entry error.

Table 12 Ophthalmological AEs Reported in Any Treatment Group (201807 Safety Population)

Preferred term, n (%)	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)[b]
Dry eye	0	1 (<1)
Eye disorder	0	1 (<1)[c]
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)

Source: Table 3.24

a. Only ophthalmological-associated events from this SOC are included.
b. Subject (b) (6) had occurrence of Wesley's immune ring.
c. The verbatim text for Subject (b) (6) was 'peripheral pigment change of left eye'.

Source: Module 5.3.5.4

All Adverse Events by Frequency
The overall incidences of AEs were similar in both treatment groups.

Table 10 AEs Reported in 1% or More of Subjects in Any Treatment Group (Safety Population)

Preferred term	Placebo N=168	TQ 300mg N=330
Subjects with any event, n (%)	**42 (25)**	**86 (26)**
Headache	9 (5)	23 (7)
Nausea	1 (<1)	14 (4)
Upper respiratory tract infection	4 (2)	8 (2)
Viral upper respiratory tract infection	4 (2)	4 (1)
Vomiting	1 (<1)	5 (2)
Back pain	2 (1)	3 (<1)
Diarrhoea	2 (1)	2 (<1)
Gastroenteritis	2 (1)	2 (<1)
Toothache	2 (1)	2 (<1)
Viral pharyngitis	2 (1)	2 (<1)
Tension headache	2 (1)	0

Source: Table 3.25

Source: Module 5.3.5.4

Best Corrected Visual Acuity (BCVA)
The absolute and change from baseline BCVA (logMAR) results and the categorical changes from baseline 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 31 BCVA Results from Assessment (Safety Population)

Data	Treatment	Eye	N	Visit	n	Mean	SD	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

Source: Table 3.16

Table 32 BCVA Change from Baseline logMAR Results (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

Source: Table 3.17

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.

Source: Module 5.3.5.4

Reviewer's Comment:

Subject (b) (6) *in the TQ group (see footnote c above) did not have a clinically significant change in visual acuity on the ETDRS acuity chart.*

Source Images

The 10% sample of source images (OCF, FA, FP) of the interim dataset (164 subjects) as JPEG files were submitted in a February 23, 2018, submission. This constituted images from 17 subjects (6 placebo and 11 TQ 300mg subjects).

Reviewer's Comment:

The submitted images were reviewed utilizing the methodology from the OCT, FAF, and the Color Form for Macular Pathology/Toxicity handbooks. These handbooks were submitted with the images as requested. The images were of sufficient quality to be read and graded by the Agency ophthalmology reviewer.

There were no disagreements with the image readings from the central image review center.

Summary/Recommendations

The results from Study 201807 do not indicate any clinically significant ocular risk from the use of 300 mg tafenoquine single dose treatment.

Consult Request Questions:

1. The Division of Anti-Infective Products requests your review and comments on the ophthalmic safety of tafenoquine which was studied in Study 201807, a phase 1, multi-center, single-masked, randomized, placebo-controlled, parallel group study to investigate the ophthalmologic safety and pharmacodynamics of 300mg single doses of tafenoquine (SB-252263) in adult healthy volunteers.

DTOP Response: *General comments regarding Study 201807 are located throughout this review. In the tafenoquine treatment group, only a single change from baseline on SD-OCT occurred and that change occurred in a patient who should have been excluded from the study due to baseline SD-OCT changes.*

The study appears to have been adequately designed and adequately conducted.

2. We ask your comments on the ophthalmic safety of tafenoquine as described in in the Summary of Clinical Safety

DTOP Response: *Review of the study report and associated representative images do not reveal any clinically significant ocular risk from the use of 300 mg tafenoquine single dose treatment.*

3. Please provide labeling recommendations based on your review of the ophthalmology data. Study

DTOP Response: *We have no recommend labeling revisions. The results from Study 201807 do not indicate any clinically significant ocular risk from the use of 300 mg tafenoquine single dose treatment.*

William M. Boyd, M.D.
Clinical Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
05/09/2018

WILEY A CHAMBERS
05/11/2018