CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210795Orig1s000

<u>OTHER REVIEW(S)</u>

Clinical Review of Request for Priority Review of NDA 210-795

Introduction
The applicant, GlaxoSmithKline, requests a priority review (NDA 210-795, submitted on 11/22/2017) for tafenoquine (TQ) for the prevention of relapse (radical cure) of *P. vivax* malaria in patients aged 16 years of age and older who are receiving appropriate therapy for acute *P. vivax* infection. TQ, an 8-aminoquinoline antimalarial drug, possesses activity against all stages of the *Plasmodium vivax* lifecycle, including the dormant liver stage, hypnozoite.

The current recommended treatment regimen for the radical cure of *P. vivax* includes a schizontocidal antimalarial, usually chloroquine (CQ), combined with a 14-day course of primaquine phosphate (PQ). TQ has slow clearance of blood stage; therefore, co-administration with another faster acting blood schizonticide (chloroquine x 3 days) is required for treatment of *P. vivax* malaria as this combination targets both blood and liver stages of infection.

The proposed dose of TQ is a single 300 mg dose, i.e. two 150 mg tablets, administered on Day 1 or Day 2 of chloroquine therapy.

PQ, approved by the FDA in 1952, is the only available drug that has activity against the liver hypnozoites of *P. vivax* (and *P. ovale*). The PQ label recommends a dose of 15mg / day for 14 days; however, the CDC recommends PQ 30mg /day for 7 to 14 days for radical cure of *P. vivax* and *P. ovale*.[1]

Regulatory Background
TQ was granted an orphan-drug designation for the treatment of malaria on January 15, 2013 and it was granted a breakthrough designation on December 18, 2013.

Priority Review Request
The applicant's rationale for a Priority Review includes:

- *P. vivax* malaria is a serious condition, as reflected in the Breakthrough Therapy Designation granted to the TQ treatment program by DAIP in December 2013.
- The only treatment option currently available to treat the liver hypnozoite parasite in *P. vivax* malaria is PQ 15 mg once daily for 14 days. Although effective if taken as instructed (administering a total dose of 210 mg), compliance with the PQ treatment regimen is poor in the real-world, which results in a sub-optimal dose, and significantly reduced clinical efficacy.
- TQ 300 mg is an effective single-dose treatment for the radical cure of *P. vivax* malaria. The simple dosing regimen will ensure compliance and an efficacious dose is administered, even in the real-world setting, resulting in improved individual and public health outcomes.
- PQ anti-malarial activity is now thought to depend on the liver enzyme CYP2D6 for conversion to an active metabolite. Unlike PQ, there is no evidence that the efficacy of TQ is negatively impacted in patients with poor/intermediate 2D6 metabolizer status,

[1] https://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf

Reference ID: 4293588

and therefore TQ potentially offers an improved therapeutic option to this subpopulation of patients.

CLINICAL REVIEW

The Qualifying criteria for priority review designation are outlined in the guidance on Expedited Programs for Serious Conditions – Drugs and Biologics.[2]

The qualifying criteria are as follows:

1. **Serious 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 and associated mortality, much of which is attributable to the chronic relapsing nature of the infection.[3,4] The burden of *P. vivax* malaria exists in countries in Southeast Asia, Africa, and South America. In 2011, the CDC reported that *P. falciparum* and *P. vivax* caused most malaria infections and were identified, respectively, in 64% and 28% of 1,490 infected persons with a reported species.[5] The World Health Organization (WHO) has developed a global strategy to control and eliminate *P. vivax* malaria. Among the WHO's specific objectives, is the review of the drugs and treatment regimens for radical cure of *P. vivax.*

Unlike *P. falciparum, P. vivax* has a hypnozoite stage in the liver 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. Chloroquine or mefloquine (used for chloroquine-resistant strains) are commonly used for treatment of the blood (erythrocytic) forms for non-falciparum malaria species such as *P. vivax*. None of these drugs have activity against hypnozoites in the liver. PQ is the only licensed drug for eradicating *P. vivax* hypnozoites and, therefore, preventing relapses of vivax malaria.

P. vivax malaria is a serious infection and the severity of disease that can be caused by *P. vivax* has been underestimated.[6] 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.[7] Splenic rupture

---

[2] Expedited Programs for Serious Conditions – Drugs and Biologics[2]
https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

[3] Howes RE, Battle KE, Mendis KN, et al. Global Epidemiology of *Plasmodium vivax*. Am J Trop Med 2016; 95(6 Suppl.):15-34.

[4] John GK, Douglas NM, von Seidlein L, et al. Primaquine radical cure of *Plasmodium vivax*: a critical review of the literature. Malar J. 2012; 11(1):280.

[5] http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6205a1.htm

[6] Kochar DK, Saxena V, Singh N, et al. *Plasmodium vivax* malaria. Emerg Infect Dis. 2005;11(1):132

[7] 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

Reference ID: 4293588

is a rare complication of acute *P. vivax* malaria and approximately 150 cases have been described.[8,9] 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. [10,11,12] *P. vivax* malaria was associated with increased morbidity and mortality in early infancy[13] in Indonesian New Guinea (Papua) and carried an elevated risk of miscarriage in the first trimester in women with acute vivax malaria in Thailand.[12]

2. **Demonstrating the potential to be a significant improvement in safety or effectiveness** on a case-by-case basis, FDA determines at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a significant improvement in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition. Significant improvement may be illustrated by the following examples:

• **Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition;**
The key studies in NDA 210-795 include a phase 2b (TAF112582-part 1) and two phase 3 trials (TAF112582-part 2 and TAF116564) to support the efficacy and safety of TQ for the treatment (radical cure) of *P. vivax* malaria in adults.
Study TAF112582-part 1 is a multicenter, double-blind, randomized, active control, dose-ranging study in adults with vivax malaria comparing chloroquine (CQ) plus TQ (dose range 50 to 600mg) to the CQ control arm and the current standard of care for radical cure, PQ (PQ) which was included as a benchmark. Analysis of the primary efficacy endpoint (recurrence-free efficacy by malaria slide read) showed evidence of efficacy for the TQ 300mg and 600mg doses. The primary endpoint i.e., recurrence- free efficacy rates at six months post-dose, was statistically significant at 89% and 92% for the TQ 300 mg and 600 mg treatment groups, respectively (Table 1). Recurrence-free efficacy rates at six months post-dose were 77% in the PQ arm and 38% in the CQ arm (a placebo-like arm, because CQ has no effect on hypnozoite liver stage). Results from this trial demonstrated that TQ as a single-dose treatment co-administered with chloroquine prevented *P. vivax* relapse/recurrence. (Molecular tests to reliably distinguish relapse from recurrence of *P. vivax* malaria are under development).

---

[8] Gockel HR, Heidemann J, Lorenz D, et al. Spontaneous splenic rupture, in tertian malaria. Infection. 2006;34(1):43.
[9] 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.
[10] 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.
[11] 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.
[12] 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.
[13] 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.

Reference ID: 4293588

Table 1. TAF112582 Part 1: Recurrence-Free Efficacy at 6 Months (Kaplan-Meier) (Intention-to-Treat Population)

	TQ 50mg (N=55)	TQ 100mg (N=57)	TQ 300mg (N=57)	TQ 600mg (N=56)	PQ (N=50)	CQ (N=54)
Relapse-free efficacy rate at 6 months, %						
Estimate	57.7	54.1	89.2	91.9	77.3	37.5
95% CI	(43,70)	(40,66)	(77,95)	(80,97)	(63,87)	(23,52)
Log Rank Test[a]						
p-value	ND	0.158	<0.0001	<0.0001	0.0004	

Source: TAF112582 Part 1 Table 22; m5.3.5.3 ISE Section 4
a. A two-sided log rank test was performed over 6 months using a 5% significance level.
ND Not done due to step-down testing procedure to adjust for multiple comparisons.

Source: Table 11 in Clinical Overview, Folder M2, NDA 210-795.

Study TAF112582-Part 2 (pivotal phase 3 efficacy study) is a multi-center, double-blind, randomized, parallel group, active-controlled study to evaluate the efficacy, safety and tolerability of TQ single-dose in subjects with *P. vivax* malaria. The primary objective was to determine the efficacy of TQ as a radical cure for *P. vivax* malaria, relative to a CQ control (a placebo - equivalent). The primary comparison was the difference in recurrence-free efficacy between 300 mg TQ+CQ and CQ alone over 6 months using the microbiologic intent-to-treat population. Both parts of TAF112582 included an arm with PQ 15 mg daily for 14 days + CQ as a benchmark.

In study TAF112582- part 2, 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. (Table 2).

Table 2. Recurrence-Free Efficacy Over 6 Months in TAF112582-Part 2 by Logistic Regression

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

Source: m5.3.5.3 ISE Section 2.1
a. Subjects with missing data were analyzed as failures.
b. Odds ratios <1 indicate a smaller chance of recurrence compared with CQ alone.

Source: Table 13 in Clinical Overview, Folder M2, NDA 210-795.

The primary objective in the second phase 3 trial, Study TAF116564, was to compare the incidence of hemolysis from treatment with TQ+CQ versus PQ+CQ. TAF116564 also provided supportive evidence of efficacy. The recurrence-free efficacy rate was estimated to be 72.7% (95% CI:64.8%, 79.2 %) in the TQ 300mg +CQ group using Kaplan-Meier methodology.

Clinical Reviewer's Comment: Neither TAF112582 Part 2 nor TAF116564 were designed to have sufficient power to make formal comparisons of efficacy (e.g., noninferiority) of TQ to PQ when co-administered with standard doses of CQ.

Reference ID: 4293588

• Elimination or substantial reduction of a treatment-limiting adverse reaction;
TQ 300mg single-dose was well-tolerated during the clinical development program. The overall safety profile of TQ at the recommended 300 mg single dose was broadly similar to that of PQ 15 mg daily for 14 days and to CQ alone for 3 days. There was no evidence that TQ exacerbates the adverse effects of CQ.

Table 3. Summary of Adverse Events with Onset on, or Prior to, Study Day 29 Reported in at Least 5% of Subjects in Any Treatment Group by Preferred Term

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

Source: m5.3.5.3 ISS Section 2.1.1
Note: PTs are listed in descending order of incidence in the TQ+CQ treatment group.

Source: Table 17 in Clinical Overview, Folder M2, NDA 210-795.

Mild 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. These differences were not considered to be clinically significant, because few subjects had hemoglobin decreases that fell in the anemic range. Clinically significant drug-induced hemolysis was not reported. Adverse events such as reversible, asymptomatic elevations in methemoglobin were observed with TQ 300 mg single-dose.

Methemoglobinemia is a class effect of 8-aminoquinolines and was observed more frequently in the CQ+ PQ treatment group. TQ had no clinically significant effect on QT at relevant doses of 300 and 600 mg compared to placebo during the development program. Retinal toxicity was not observed in an interim analysis of the ophthalmic safety of single-dose TQ in study 201807. Benign, reversible vortex keratopathy has been reported in TQ studies following long-term therapy (~ 6 months) or supra-therapeutic dosing; however, vortex keratopathy was not observed in any subjects included in this interim analysis for study 201807. No serious psychiatric adverse reactions were reported in clinical trials of TQ single-dose (300mg) for treatment of *P. vivax* malaria; however, cases of depression and psychosis have been reported following higher single doses (350 to 600 mg), mostly in patients with a history of psychiatric disorders.

Clinical Reviewer's Comment: The elimination or substantial reduction of a treatment-limiting adverse reaction was not observed in the phase2/3 clinical trials of TQ. The overall safety profile of TQ at the recommended 300 mg single dose was broadly similar to PQ. The principal safety risk of TQ and PQ is that both drugs can cause hemolysis in subjects with G6PD deficiency. TQ and PQ must not be prescribed to subjects with G6PD enzyme level activity

Reference ID: 4293588

<70% of normal. There remains an unmet medical need for a safe antimalarial drug for radical cure of P. vivax and P. ovale malaria in patients with G6PD deficiency.

• Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes

Adherence to chloroquine and PQ is vital in achieving full effectiveness of the treatment of *P. vivax* malaria. Compliance in the clinical trials, TAF112582 Part 2 and TAF116564, was ≥ 96% for both TQ+CQ and PQ+CQ treatments, which is high compared to the level of adherence to PQ in real-life. The generalizability of compliance in a randomized controlled trial to real-life is questionable because subjects behave differently outside the context of a trial.
Douglas, *et al* reported that PQ is substantially less effective for preventing relapse (causal prophylaxis) of vivax malaria in real-world practice than is predicted by clinical efficacy trials and that this is a likely consequence of incomplete adherence to treatment. Overall, the risk of re-presentation with vivax malaria was 37.2% (95%CI 35.6%–38.8%) in patients in Southern Papua who were prescribed no primaquine compared to 31.6% (95%CI 30.9%–32.3%) in those who self-administered either a low (_≥1.5 mg/ kg and < 5 mg/kg) or high (_≥5 mg/kg) dose of primaquine (AHR = 0.90 [95%CI 0.86–0.95, $p < 0.001$]). Limiting the comparison to high dose versus no primaquine in the period during and 12 months before and after a large stock outage resulted in minimal change in the estimated clinical effectiveness of primaquine (AHR 0.91, 95%CI 0.85–0.97, $p = 0.003$).[14]

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.[15,16,17,18] Adherence has been reported to be low (60%) even with a shorter 7-day course of PQ offered for free.[19]
A single dose of TQ should improve compliance as compared to the 7- or 14-day course of PQ.

Clinical Reviewer's Comment: Preventing relapse of P. vivax is a vital component of achieving cure in an individual patient and in global malaria elimination efforts. Improved education of patients and the availability of a rapid and accurate test for G6PD status at the point of care are crucial to this endeavor.[20] *The applicant provided evidence from published literature that nonadherence of PQ is related to treatment failures in P. vivax malaria. TQ as a single dose for*

---

[14] Douglas NM, Poespoprodjo JR, Patrianai D, et al. Unsupervised primaquine for the treatment of Plasmodium vivax malaria relapses in southern Papua: A hospital-based cohort study. PLOs Medicine 2017;14(8): e1002379
[15] Pereira EA, Ishikawa EA, Fontes CJ. Adherence to *Plasmodium vivax* malaria treatment in the Brazilian Amazon Region. Malar J. 2011;10:355.
[16] Maneeboonyang W, Lawpoolsri S, Puangsa-Art S, et al. Directly observed therapy with primaquine 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
[17] Takeuchi R, Lawpoolsri S, Imwong M, et al. Directly-observed therapy (DOT) for the radical 14-day primaquine treatment of Plasmodium vivax malaria on the Thai-Myanmar border. Malar J. 2010;9:308.
[18] 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.
[19] Grietens KP, Soto V, Erhart A, et al. Adherence to 7-day primaquine treatment for the radical cure of *P. vivax* in the Peruvian Amazon. Am J Trop Med Hyg. 2010;82:1017–23.
[20] Thriemer K, Ley B, Bobogare A, et al. Challenges for achieving safe and effective radical cure of P. vivax: a round table discussion of the APMEN Vivax Working group. Malaria J 2017;16:141 DOI 10.1186/s12936-017-1784-1

Reference ID: 4293588

radical cure of P. vivax would be a major improvement over the 7- to 14-day course of PQ. One disadvantage is the long elimination half-life of TQ; if drug-induced signs of hemolysis occur, treatment can't be curtailed by stopping drug administration as is currently the case with PQ. However, an improvement in compliance with single-dose TQ could improve clinical outcomes by reducing subsequent relapse of P. vivax malaria, reduce transmission within communities and, if used widely, could possibly help to reduce the global burden of P. vivax malaria.

The criterion "*documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes" is fulfilled based on published literature which demonstrated that compliance with the 14- day course of PQ is low in real-world practice, and that this lack of compliance leads to relapses of vivax malaria and morbidity in the infected individual. In effect these data external to the trial were used to support relying on an external control to demonstrate a compliance advantage that translates to a clinical benefit. In addition, a drug such as TQ, by improving patient compliance has the potential to help public health efforts to eliminate P. vivax malaria by reducing its transmission in endemic areas.*

• Evidence of safety and effectiveness in a new subpopulation

The FDA guidance on Expedited Programs for Serious Conditions [2] also states that, "Although such evidence [to support a priority review] can come from clinical trials comparing a marketed product with the investigational drug, a priority review designation can be based on other scientifically valid information. Generally, if there is an available therapy, sponsors should compare their investigational drug to the available therapy in clinical testing with an attempt to show superiority relating to either safety or effectiveness. Alternatively, sponsors could show the drug's ability to effectively treat patients who are unable to tolerate, or whose disease failed to respond to, available therapy or show that the drug can be used effectively with other critical agents that cannot be combined with available therapy. Although such showings would usually be based on randomized trials, other types of controls could also be persuasive, for example, historical controls."

Clinical Reviewer's Comment: The NDA does not contain sufficient safety or effectiveness data for TQ in a new subpopulation. The applicant was unable to recruit enough patients with G6PD deficiency in the 40 to 70% range to evaluate this subpopulation for hematological adverse events such as hemolysis in Study TAF116564. Therefore, from what is known now about TQ, it should be contraindicated in patients with G6PD deficiency or unknown G6PD status until it can be further evaluated. Neither PQ nor TQ can be administered to pregnant women (the G6PD status of the fetus is unknown) or patients with G6PD deficiency.

PQ metabolism is complex and thought in part to be mediated by CYP2D6, which contributes to PQ conversion to its active metabolite.[21] Patients who are poor or intermediate 2D6 metabolizers may have suboptimal exposure to the active metabolite of PQ and in turn, may have poor response to PQ treatment; however, this finding has not been adequately evaluated in clinical trials. In current clinical practice, it is not feasible to test individuals for 2D6 metabolizer status prior to dosing with PQ.

---

[21] Marcsisin SR, Reichard G, Pybus BS. Primaquine pharmacology in the context of CYP2D6 pharmacogenomics: Current stat of the art. Pharmacol & Therapeutics 2016;161-1-10.

Reference ID: 4293588

An analysis of the efficacy results in the subgroup of patients who had normal versus poor/intermediate 2D6 metabolizer status by treatment arms in the phase 3 trial, TAF112582 part 2, is summarized in Table 4.

Table 4. Study TAF112582 part 2: Subjects with relapse/recurrence-free efficacy at 6 months (primary analysis) by CYP2D6 metabolizer status

CYP2D6 metabolizer	*PQ+CQ*	*TQ+CQ*	*CQ only*
All	83/129 (64.3%)	155/260 (59.6%)	35/133 (25.5%)
Extensive metabolizer	58/87 (66.7%)	112/192 (58.3%)	18/94 (19.1%)
Intermediate metabolizer	22/35 (62.9%)	33/54 (61.1%)	15/34 (44.1%)
Poor metabolizer	0/3 (0)	2/3 (66.7%)	0/2 (0)
Intermediate or poor	22/38 (57.9%) 16.2% [-6.3%, 38.7%] p-value=0.163	35/57 (61.4%) 19.7% [-0.7%, 40.2%] p-value=0.063	15/36 (41.7%)
Extensive versus intermediate or poor	-8.8% [-27.3%, 9.8%] p-value=0.10	3.1% [-11.4%, 17.5%] p-value=0.68	22.5% [4.6%, 40.5%] p-value=0.008

Source: Analysis conducted by biostatistics reviewer, Xianbin Li, Ph.D.

The point estimate for relapse/recurrence-free efficacy at 6 months is higher for PQ+CQ than TQ+CQ in intermediate metabolizers and there are only 3 subjects per arm in the poor metabolizer group. These results are not statistically significant and do not provide adequate support for the applicant's argument that TQ may have an efficacy advantage over PQ in subjects who are CYP2D6 poor/intermediate metabolizers.
Presently, there is no evidence that CYP2D6 polymorphisms impact TQ efficacy; however, a potential TQ advantage over PQ in this subgroup would need to be further evaluated.

Summary and Recommendation

The available evidence from the clinical trials of TQ does not support a safety or efficacy advantage over the approved drugs for *P. vivax* malaria treatment. However, TQ has a potential advantage over current therapy with regard to patient compliance, which is supported by data from published literature. Adherence to treatment for *P. vivax* malaria should improve with CQ plus a single-dose of TQ as compared to CQ plus a 7- to 14-day course of PQ. An improvement in compliance with treatment could improve clinical outcomes by reducing relapses of *P. vivax* malaria and its associated morbidity and could reduce transmission in malaria endemic areas and possibly reduce the global burden of vivax malaria.

This clinical reviewer recommends a priority review for NDA 210-795 based on the potential of TQ (single-dose) to improve compliance with treatment (radical cure) of *P. vivax* malaria.

Reference ID: 4293588

Addendum:
Medical Policy and Program Review Council (MPPRC)
On January 10th, 2018, the Division sought advice from the MPPRC on the priority review request for NDA 210795

The Division briefed the Council on the supportive evidence provided by the applicant and published literature on the lack of patient compliance with PQ therapy for radical cure of *P. vivax* malaria as discussed above.

The Council agreed that the published literature submitted by the applicant was sufficient to support the request for priority review based on 1) a potential compliance advantage for a TQ single dose over the current 14-day course of primaquine with the potential for improved clinical outcomes and 2) the important public health implications for possible reduced transmission of vivax malaria in malaria endemic areas. The Council acknowledged the challenges of demonstrating an outcome advantage due to improved compliance in the clinical trials and opined that the literature could be used as the basis for the priority review decision.

Note: The briefing document for the MPPRC meeting held on Jan 10th 2018 is in DARRTS.

Reference ID: 4293588

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/

ELIZABETH M OSHAUGHNESSY
07/18/2018

YULIYA I YASINSKAYA
07/18/2018

SUMATHI NAMBIAR
07/19/2018

Clinical Inspection Summary

Date	July 18, 2018
From	John Lee, M.D., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Gregory DiBernardo, Regulatory Project Manager Elizabeth O'Shaughnessy, M.D., Medical Officer Yuliya Yasinskaya, M.D., Clinical Team Leader Sumati Nambiar, M.D., M.P.H., Director Division of Anti-Infective Products (DAIP)
Application	NDA 210795
Applicant	GlaxoSmithKline Intellectual Property Development Ltd. England
Drug	Tafenoquine (Krintafel®)
NME / Original NDA	Yes
Review Status	Priority
Proposed Indication	Prevention of P. vivax malaria relapse in patients 16 years old or older
Consultation Date	January 16, 2018
CIS Goal Dates	April 18 (inspection planning) and July 18 (after inspections), 2018
Action Goal Date	July 22, 2018
PDUFA Due Date	July 22, 2018

I. OVERALL ASSESSMENT OF FINDINGS

Study TAF112582 was audited at good clinical practice (**GCP**) inspections of two foreign clinical investigator (**CI**) sites selected based on: (1) no 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.

II. BACKGROUND

GlaxoSmithKline Intellectual Property Development Ltd. England (**GSK**) proposes the use of tafenoquine (Krintafel®) for the "radical cure" (prevention of relapse) of Plasmodium vivax (**P. vivax**) malaria in adults and adolescents 16 years of age and older.

Malaria is a parasitic infection (by Plasmodium) primarily of the red blood cell transmitted by mosquitoes. Unlike P. falciparum, P. vivax has a latent liver phase (and disease relapse), and the only currently available therapy against the liver stage parasite (hypnozoite) is a 14-day course of daily oral primaquine (**PQ**). Treatment efficacy is reduced 3-fold when ≥ 3 missed doses. Treatment of the blood stage (schizont) infection using quinine, chloroquine, and/or artemisinin does not clear the hypnozoites (relapse days/years later).

Tafenoquine (**TQ**) is an anti-malarial agent active against the liver hypnozoite, with a half-life of 15 days which allows adequate treatment using a single oral dose when used in combination with a (3-day) course of chloroquine (**CQ**) or other blood stage anti-malarial agent. In Study TAF 112582 (to be audited), the primary objective was to determine the recurrence-free efficacy of a single 300 mg dose of TQ + CQ, relative to CQ alone. A PQ arm (15 mg/day x 14 days) served as a statistically non-powered reference. Subjects with parasitemia clearance, no evidence of hypnozoite, and a peripheral blood smear (**PBS**) negative for P. vivax at 6 months were considered successfully treated (cured).

Study TAF 112582: *A multi-centre, double-blind, randomized, parallel-group, active-controlled study to evaluate the efficacy, safety and tolerability of tafenoquine (SB-252263, WR238605) in subjects with Plasmodium vivax malaria*

This double-blind, randomized, active-controlled study was conducted between 2014 - 2016 in 6 foreign countries (Brazil, Peru, Ethiopia, Cambodia, Philippines, Thailand) in 522 subjects at 8 CI sites. The primary study objective was to evaluate recurrence-free efficacy for the radical cure of P. vivax malaria at six months after a single oral dose of tafenoquine, as assessed by light microscopy of serial PBSs. Subjects were randomized to three treatment arms in 1-2-1 ratio, respectively: CQ alone, TQ+CQ, and PQ+CQ. Subjects were treated/evaluated for 14 days, in the clinic for Days 1-3 or until parasite clearance was confirmed, then as outpatients for the remainder of the study and followed for up to 180 days. Subjects of age ≥ 16 years were selected for:

- PBS positive for P. vivax (thick prep, Giemsa stain)
- Schizont density between 100 and 100,000 per microliter of blood
- Glucose 6-phosphate dehydrogenase (**G6PD**) enzyme activity > 70% of normal

Subjects excluded for mixed or severe P. vivax malaria infections, screening hemoglobin < 7 g/dL, allergy to study medication or any aminoquinoline, liver enzyme (alanine aminotransferase) over twice normal upper limit, severe vomiting, past medical history (porphyria, psoriasis, epilepsy, or significant cardiovascular disease), or current/recent treatment with protocol-prohibited medications.

All subjects received CQ open-label for the first 3 days (600 mg on Days 1 and 2, 300 mg on Day 3). On Day 1 and/or Day 2, subjects received: (1) TQ (300 mg) as a single dose followed by placebo for the remainder of 14 days, or (2) PQ (15 mg) once daily for 14 days.

III. INSPECTION OUTCOMES

Inspected Entity	Study / Site Enrollment	Inspection Dates	Inspection Outcome
Marcus Vinicius de Lacerda, M.D. Avenida Pedro Teixeira, 25 Manaus Amazonas, Brazil	TAF112582 Site 87400 196 subjects	June 18 – 22, 2018	NAI
Srivicha Krudsood, M.D., Ph.D. University Dept of Tropical Hygiene OPD Building, 420/6 Ratchawithi Rd Ratchathewi, Bangkok, Thailand	TAF112582 Site 87111 58 subjects	June 25 – 28, 2018	VAI*

CI site selection: only foreign sites in study, high subject enrollment, and inspection feasibility

Compliance Classification of Inspection Outcome

NAI = No Action Indicated, no significant deviations from regulations
VAI = Voluntary Action Indicated, minor deviations from regulations
OAI = Official Action Indicated, major deviations from regulations

* For CI Krudsood (Bangkok, Thailand), the complete establishment inspection report (**EIR**) has not been received from the field office. The inspection outcome shown is based on preliminary review of all available information, including verbal communication with the field investigator. An addendum to this clinical inspection summary (**CIS**) will be forwarded to the review division if new significant findings are discovered at completion of EIR review; otherwise, OSI's written letter to the inspected entity (to be copied to DAIP) indicates completion of EIR review with confirmation of the findings as reported in this CIS.

1. Marcus Vinicius de Lacerda, M.D.

Study TAF112582, Site 87400: 245 subjects were screened, 197 were enrolled, and 194 completed the study. Case records were reviewed in detail for 48 randomly identified subjects. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, subject discontinuation, AEs, protocol deviations, major efficacy endpoints, and concomitant antibiotic medication use.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared GCP-compliant, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

2. Srivicha Krudsood, M.D., Ph.D.

Study TAF112582, Site 87111: 65 subjects were screened, 58 were enrolled, and 56 completed the study. Case records were reviewed in detail for 28 randomly identified subjects. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, subject discontinuation, AEs, protocol deviations, major efficacy endpoints, and concomitant antibiotic medication use.

A Form FDA 483 was issued for a single isolated deficiency observation. For 9 of 58 (16%) enrolled subjects, 19 semi-quantitative determinations of the parasite concentration in the peripheral blood (malaria counts) were inaccurate, as determined by light microscopy of PBS (mean of two determinations by independent microscopists).

- The inaccurate malaria counts were typically for pre-treatment or early post-treatment evaluations, to confirm parasitemia pre-treatment as part of subject selection or to evaluate parasite clearance (efficacy) over the first three days of treatment.
- The inaccurate counts appeared to be mostly from human errors, data entry errors and/or data calculation errors in converting the raw microscopy count into malaria count (parasite concentration) in the peripheral blood. The errors appeared random (unbiased).

Study conduct otherwise appeared GCP-compliant, including sponsor oversight monitoring of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice K. Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Document Room / NDA 210795
DAIP / Division Director / Sumathi Nambiar
DAIP / Clinical Team Leader / Yuliya Yasinskaya
DAIP / Medical Officer / Elizabeth O'Shaughnessy
DAIP / Regulatory Project Manager / Gregory DiBernardo
OSI / Office Director / David Burrow
OSI / DCCE / Division Director / Ni Khin
OSI / DCCE / GCPAB / Branch Chief / Kassa Ayalew
OSI / DCCE / GCPAB / Team Leader / Janice Pohlman
OSI / DCCE / GCPAB / Medical Officer / John Lee
OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / Database Project Manager / Dana Walters

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/

JONG HOON LEE
07/17/2018

JANICE K POHLMAN
07/17/2018

KASSA AYALEW
07/17/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 22, 2018
To:	Sumathi Nambiar, MD, MPH Director **Division of Anti-Infective Products (DAIP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	David Foss, Pharm. D., MPH, BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	KRINTAFEL (tafenoquine)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 210795
Applicant:	GlaxoSmithKline LLC (GSK)

1 INTRODUCTION

On November 22, 2017, GlaxoSmithKline LLC (GSK) submitted for the Agency's review a 505(b)(1) original New Drug Application (NDA) 208251 for KRINTAFEL (tafenoquine) tablets, for oral use. The proposed indication for KRINTAFEL (tafenoquine) tablets, for oral use is for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients aged (b) (4) years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infective Products (DAIP) on March 6, 2018 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for KRINTAFEL (tafenoquine) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft KRINTAFEL (tafenoquine) tablets, for oral use PPI received on November 22, 2017 and received by DMPP on June 11, 2018.
- Draft KRINTAFEL (tafenoquine) tablets, for oral use PPI received on November 22, 2017 and received by OPDP on June 11, 2018.
- Draft KRINTAFEL (tafenoquine) tablets, for oral use Prescribing Information (PI) received on November 22, 2017, revised by the review division throughout the review cycle, and received by DMPP on June 11, 2018.
- Draft KRINTAFEL (tafenoquine) tablets, for oral use Prescribing Information (PI) received on on November 22, 2017, revised by the review division throughout the review cycle, and received by OPDP on June 11, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

6 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

----

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NYEDRA W BOOKER
06/22/2018

DAVID F FOSS
06/22/2018

MARCIA B WILLIAMS
06/25/2018

LASHAWN M GRIFFITHS
06/25/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 22, 2018

To: Elizabeth O' Shaughnessy, M.D.
Division of Anti-Infective Products (DAIP)

Gregory DiBernardo, Regulatory Project Manager, (DAIP)

Abimbola Adebowale, Associate Director for Labeling, (DAIP)

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for KRINTAFEL (tafenoquine) tablets, for oral use

NDA: 210795

In response to DAIP's consult request dated March 6, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and carton and container labeling for the original NDA submission for (Krintafel).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DAIP on June 11, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on June 22, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAIP on June 13, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

22 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 4281813

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID F FOSS
06/22/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: May 21, 2018 **Date consulted:** March 27, 2018

From: Jane Liedtka M.D., Medical Officer (MO), Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Elizabeth O'Shaughnessy M.D., MO,
Office of Antimicrobial Products (OAP),
Division of Anti-Infective Products (DAIP)

Drug: Krintafel (tafenoquine)

NDA: 210795

Applicant: Glaxo Smith Kline Intellectual Property Development Ltd England (GSK)

Subject: Pregnancy and Lactation Labeling [new NDA, priority review (The Program), breakthrough, orphan]

Proposed Indication:

Tafenoquine (TQ) is an 8-aminoquinolone anti-malarial that is indicated for the radical cure (prevention of relapse) of *Plasmodium vivax* (PV) malaria in adults and adolescents 16 years and older [with a single oral 300 mg dose of tafenoquine taken in conjunction with a course of chloroquine (or other appropriate blood stage anti-malarial in a region with chloroquine resistance)]

Reference ID: 4266131

Materials Reviewed:

- Applicant's submitted background package for NDA 210795 submitted on November 22, 2017

INTRODUCTION AND BACKGROUND

On November 22, 2017, the applicant (GSK) submitted an original 505 (b)(1) new drug application (NDA) for Krintafel (tafenoquine), NDA 210795. DAIP consulted DPMH on March 27, 2018, to assist with the Pregnancy and Lactation subsections of labeling.

- Tafenoquine (TQ) is an 8-aminoquinolone anti-malarial indicated for the radical cure (prevention of relapse) of Plasmodium vivax (PV) malaria.
- Same pharmacologic class as Primaquine (NDA 8316), approved on January 23, 1952.

REVIEW
PREGNANCY

Malaria and Pregnancy

- Malaria infection during pregnancy is a major public health problem worldwide, with 50 million pregnancies exposed to the infection every year[1].
- Approximately 25,000 maternal deaths and between 75,000 and 200,000 infant deaths could be prevented each year by effective malaria control in pregnancy[2].
- According to the Center for Disease Control (CDC)[3], malaria infection in pregnant women can be more severe than in non-pregnant women. Malaria increases the risk for adverse pregnancy outcomes, including prematurity, spontaneous abortion, and stillbirth. For these reasons, and because no chemoprophylaxis regimen is completely effective, women who are pregnant or likely to become pregnant should be advised to avoid travel to areas with malaria transmission if possible. If travel to a malarious area cannot be deferred, use of an effective chemoprophylaxis regimen is essential.
- Current World Health Organization (WHO) recommendations for the control of Malaria in Pregnancy (MIP) in areas of stable [high] transmission include intermittent preventive treatment (IPT) with at least two treatment doses of sulfadoxine—pyrimethamine (SP).
- Non-infected pregnant women traveling to areas where chloroquine-resistant P. falciparum has not been reported may take chloroquine prophylaxis. For travel to areas where chloroquine resistance is present, mefloquine is the only medication recommended for malaria chemoprophylaxis during pregnancy. In 2011, the FDA reviewed available data for mefloquine use during pregnancy and reclassified it from category C to category B.
- Current recommendations from the WHO for the control of MIP based on region are displayed below in Table1.

---

[1] WHO. A strategic framework for malaria prevention and control during pregnancy in the African region. WHO, Geneva 2004, 2004: AFR/MAL

[2] van Geertruyden JP *et al*. The contribution of malaria in pregnancy to perinatal mortality. Am J Trop Med Hyg. 2004; 71:35-40

[3] CDC- Chemoprophylaxis during pregnancy and breastfeeding. Accessed 4/10/18. https://wwwnc.cdc.gov/travel/yellowbook/2018/advising-travelers-with-specific-needs/pregnant-travelers.

Reference ID: 4266131

Table 1: Currently recommended drugs for treatment and Prevention of Malaria in Pregnancy by WHO region

Region	*P. falciparum*				*P.vivax*	
	Treatment				Prevention Treatment	
	Uncomplicated		Severe			
	1st Trimester (T)	2 – 3rd T	1st T	2 – 3rd T		
Africa	QN + clindamycin*	ACT[Y]	QN/AS	AS	IPTp–SP[♪]	CQ[#]
Americas	QN + clindamycin* (or CQ**)	ACT or MQ		or	NA	CQ[zz]
Eastern Mediterranean	QN + clindamycin*	ACT[§§]		AM	NA[♪♪]	
Europe	-			or	NA	
South-east Asia	QN + clindamycin* (or CQ**)	Act		QN[§]	NA	
Western Pacific	QN + clindamycin*	ACT			CQ weekly[##]	

WHO World Malaria report 2008 and WHO Malaria treatment guidelines 2006.

ACT: Artemisinin-based combination therapy; AM: Artemether; AS: Artesunate; CQ: Chloroquine; IPTp: Intermittent preventive treatment in pregnancy; MQ: Mefloquine; NA: Not adopted; QN: Quinine; SP: Sulfadoxine--pyrimethamine; T: Trimester. *If clindamycin is unavailable or unaffordable, then QN monotherapy should be given.

[Y]ACTs being adopted in the African region are artemether–lumefantrine (Angola, Benin, Bostwana, Burkina Faso, Central African Republic, Comoros, Ethiopia, Gambia, Guinea-Bissau, Kenya, Malawi, Mozambique, Namibia, Niger, Nigeria, Rwanda, South Africa, Tanzania, Togo, Uganda, Zambia, Zimbabwe) and artesunate + amodiaquine (Burundi, Cameroon, Chad, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Ghana, Guinea, Liberia, Madagascar, Mauritania, Sao Tome and Principe, Senegal, Sierra Leone). CQ is used in Cape Verde and Swaziland, CQ + SP in Eritrea. Some of these countries have not yet implemented these current policies.

[§]Parenteral administration. Where available, AS is the first, and AM the second option for treating severe malaria during pregnancy in the second and third trimesters.

[♪]Chloroquine + proguanil is given in Bostwana, South Africa and Swaziland instead of IPTp with SP. In Cape Verde, CQ weekly is policy for preventing malaria in pregnancy.

[#]CQ is recommended in Algeria, Ethiopia and Mauritius, where the malaria parasite is CQ sensitive.

**CQ is indicated for the treatment of *P. falciparum* infections in areas where the parasite is CQ sensitive (e.g. Guatemala, Myanmar).

[zz]CQ is given for treatment and then weekly until delivery; primaquine is contraindicated in pregnancy and is administered only after delivery. [§§]AS + SP is given in Dijibouti, Pakistan, Somalia, Sudan and Yemen; CQ + SP is indicated in Afghanistan [♪♪] IPTp with SP is the policy in Somalia and Sudan.

[##]Weekly prophylaxis with CQ is recommended drug policy for prevention of malaria in pregnancy in Malaysia, Papua New Guinea, Philippines, Vanuatuand Vietnam.

Source: Sevene *et al*[4] pg. 1287

Nonclinical Experience

There were increased abortions, with and without maternal toxicity when KRINTAFEL was given orally to pregnant rabbits at and above doses equivalent to about 0.4 times the clinical exposure based on body surface area comparisons. In a similar study in rats, doses of 3, 10, or 30 mg/kg/day resulted in maternal toxicity (enlarged spleen, reduced body weight and reduced food intake) at the high-dose. There was no evidence of malformations in either species. The reader is referred to the full Pharmacology/Toxicology review by Owen McMaster, PhD.

[4] Sevene E *et al.* Current knowledge and challenges of antimalarial drugs for treatment and prevention in pregnancy. 2010. Expert Opinion on Pharmacotherapy, 11:8, 1277-1293.

Reference ID: 4266131

Review of Pharmacovigilance Database
No review of the pharmacovigilance database was performed. The Integrated Summary of Safety for the development program for Krintafel notes that

> There were 3 pregnancies reported in subjects receiving TQ in the primary studies. One subject underwent an elective abortion (TAB) and one withdrew consent and was lost to follow-up. The third subject had a spontaneous abortion at approximately six weeks gestation, based on an ultrasound at Study Day 19.

Applicant's Review of Literature
The applicant did not provide a review of the literature.

DPMH's Review of Literature
DPMH conducted a search of published literature in PubMed and Embase on April 9, 2018 using the search terms "tafenoquine and pregnancy," "tafenoquine and pregnant women," "tafenoquine and pregnancy and birth defects," "tafenoquine and pregnancy and congenital malformations," "tafenoquine and pregnancy and stillbirth," "tafenoquine and spontaneous abortion" and "tafenoquine and pregnancy and miscarriage." No reports of adequate and well-controlled studies of tafenoquine use in pregnant women were found. No published case reports involving pregnancy in tafenoquine patients were identified. A few general articles on the treatment of malaria during pregnancy were identified and were cited earlier in this review in the section entitled "Malaria and Pregnancy".

Tafenoquine is referenced in MicroMedex[5] under investigational products, the authors' state

> Tafenoquine is an 8-aminoquinoline antimalarial and more lipophilic derivative of primaquine. It acts as a tissue schizontocide and is under investigation as the succinate for the radical cure and prevention of relapse in vivax malaria. It may also have a role in the prophylaxis of falciparum malaria. Although it has been suggested to be better tolerated than primaquine, tafenoquine still carries a risk of hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient patients.

Reviewer comment:
The Applicant notes that they have modeled their proposed labeling after primaquine labeling due to the fact that their product is closely related in structure and is expected to have similar effects. Therefore, I have accessed the relevant information on primaquine in several sources.

In the MicroMedex[5] statement for primaquine, the authors note "fetal risk has been demonstrated" and state

> The CDC recommend that primaquine not be administered during pregnancy because of the possibility the fetus may be G6PD-deficient, especially in pregnant

[5] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 4/9/18.

Reference ID: 4266131

> patients at risk for this disorder[6]. Perform a pregnancy test prior to therapy initiation in women of reproductive potential. Advise women to avoid pregnancy during administration of primaquine. Advise sexually-active women to use effective contraception during and until after stopping treatment until completion of an ongoing ovulatory cycle (e.g., up to next menses). Advise men to avoid fathering a child and to use condoms during and for 3 months after completing treatment[7].

Similarly, in *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk,*[8] the authors' state

> No reports describing the use of primaquine in human pregnancy have been located. Primaquine may cause hemolytic anemia in patients with G6PD deficiency… Because the fetus is relatively G6PD-deficient, the drug should not be used in pregnancy regardless of the mother's status[9,10,11].

Reviewers comment:
Like primaquine, tafenoquine may cause hemolytic anemia if taken by a person with G6PD deficiency. Current labeling for primaquine and proposed labeling for tafenoquine contraindicates the use of these products during pregnancy due to the potential for hemolytic anemia in the event that the fetus has G6PD deficiency.

The embryologic development of the circulatory system begins early; the heart has developed enough by day 21 post-fertilization to begin beating. Circulation patterns are clearly established by the fourth week of embryonic life. [12]*The possibility of an inadvertent exposure early in pregnancy (during the window before a pregnancy test becomes positive or in the event of a false negative pregnancy test) still exists. Given the lack of teratogenicity in animal studies and the time that is takes for the development of a circulatory system with red blood cells that may be affected by hemolysis, DPMH recommends a Warning and Precaution for Embryofetal Toxicity instead of Contraindication for Pregnancy.*

LACTATION

<u>Nonclinical Experience</u>
There are no animal studies of tafenoquine during lactation.

---

[6] Arguin PM and Tan KR: Malaria. In: Centers for Disease Control and Prevention (CDC), Brunette GW, eds. CDC Health Information for International Travel 2018 Yellow Book, Oxford University Press, New York, NY, 2017.
[7] Product Information: primaquine phosphate oral tablets, primaquine phosphate oral tablets. Sanofi-Aventis US LLC (per FDA), Bridgewater, NJ, 2017.
[8] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2015). Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.
[9] Phillips-Howard PA, Wood D. The safety of antimalarial drugs in pregnancy. Drug Saf 1996; 14:131-45.
[10] Nosten F *et al*. Antimalarial drugs in pregnancy: a review. Curr Drug Saf 2006; 1:1-15.
[11] Irvine MH, Einarson A, Bozzo P. Prophylactic use of antimalarials during pregnancy. Can Fam Physician 2011; 57:1279-81.
[12] https://courses.lumenlearning.com/suny-ap2/chapter/development-of-blood-vessels-and-fetal-circulation/

Reference ID: 4266131

Applicant's Review of Literature
The applicant did not provide a review of the literature.

DPMH's Review of Literature
DPMH conducted a search of *Medications and Mother's Milk*[13], Micromedex[5], LactMed[14] and of published literature in PubMed and Embase using the search terms "tafenoquine and lactation" and "tafenoquine and breastfeeding." No relevant data were found.

According to the proposed label, the molecular weight of tafenoquine is ≈ 582 Daltons as the succinate salt and ≈ 464 Daltons as the free base and is highly protein bound (> 99.5%). The average terminal half-life is ≈ 15 days. Common adverse reactions (≥5%) were dizziness, nausea, vomiting, headache, and decreased hemoglobin. Proposed Warnings for the label for tafenoquine include hemolytic anemia, methemoglobinemia, serious psychiatric reactions and serious hypersensitivity reactions and G6PD testing is mandatory before administration.

Pharmacokinetic information for primaquine (a closely related medication) includes a molecular weight of ≈ 259, a half-life of 6 hours, bioavailability of 96% and protein binding of 20%.

The relevant "Summary of Use" information on primaquine in LactMed[13] states

> Primaquine is poorly excreted into breastmilk of nursing mothers and undetectable in the serum of their breastfed infants. Breastfed infants beyond the neonatal period have shown no evidence of hemolysis, but neonates and those with glucose-6-phosphate dehydrogenase (G6PD) deficiency have not been studied. If primaquine is required, the mother and infant should be tested for G6PD deficiency before primaquine is given to a nursing mother.
>
> United Kingdom malaria treatment guidelines recommend that primaquine be avoided in nursing mothers with malaria and that weekly chloroquine 500 mg be given until breastfeeding is completed[15]. However, these guidelines were developed before information on the excretion of primaquine into breastmilk and safety in breastfed infants was published. The Centers for Disease Control and Prevention guidelines state that primaquine may be used in breastfeeding mothers and infants with normal G6PD levels[16,17]. Because the small amounts of primaquine transferred in breast milk are insufficient to provide adequate

[13] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing.
[14] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 4/9/18.
[15] Lalloo DG *et al*. UK Malaria Treatment Guidelines 2016. J Infect. 2016; 72:635-49.
[16] CDC Yellow Book 2018: Health Information for International Travel. New York: Oxford University Press. 2017.
[17] Gilder ME *et al*. Primaquine pharmacokinetics in lactating women and breastfed infant exposures. Clin Infect Dis. 2018.

Reference ID: 4266131

protection or treatment of malaria, infants who require chemoprophylaxis or therapy must receive the recommended dosages of primaquine.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

In a rat fertility study, tafenoquine was given orally at about 0.5 times the human dose based on body surface area comparisons to males for at least 67 days, including 29 days prior to mating, and to females from 15 days prior to mating through early pregnancy. Tafenoquine resulted in reduced number of viable fetuses, implantation sites in the presence of maternal toxicity (mortality, piloerection, rough coat, and reduced body weight). The reader is referred to the full Pharmacology/Toxicology review by Owen McMaster, PhD.

DPMH's Review of the Literature

DPMH conducted a search of published literature in PubMed and Embase regarding tafenoquine and its effects on fertility and found no relevant literature. However, the Applicant proposes pregnancy testing and contraception recommendations to be included in Section 8.3. DPMH agrees with this proposal. See DPMH proposed labeling for details.

DISCUSSION AND CONCLUSIONS

Pregnancy

There are very little data on human exposure to Krintafel during pregnancy (3 exposures, no births). Teratogenicity was not seen in animal studies but increased abortions (mostly in the presence of maternal toxicity-there was only one abortion below maternally toxic doses) were seen at doses below human equivalents.

The major issue of concern is the potential for hemolysis in a G6PD-deficient fetus (which theoretically can occur even in the presence of a G6PD normal mother). (b) (4) Given that the concern is a theoretical one that has not actually been demonstrated, DPMH recommends (b) (4) the following:

1. A Warning for embryofetal toxicity
2. A recommendation for pregnancy testing prior to administration of tafenoquine
3. A recommendation for contraception use in females of reproductive potential during administration of tafenoquine.

Lactation

There is no information available regarding the presence of tafenoquine in human or animal milk. Only recently (in 2018) results of studies on primaquine in human milk were published which document that primaquine is very poorly excreted into human milk and levels were undetectable in infants[15, 16]. Tafenoquine is a larger molecule than primaquine (464 vs 259) and has very high

Reference ID: 4266131

protein binding (>99%) which would suggest it is even less likely to be excreted in significant amounts into human milk. However, if it is present even in small amounts, the very long half-life (15 days) raises the possibility of tafenoquine accumulating in the infant's plasma.

With regard to breastfeeding, if the full-term infant has normal levels of G6PD upon testing, breastfeeding can be considered, keeping in mind that with the long half-life of tafenoquine means whatever exposure does occur will not be resolved for almost 3 months even with a one-time exposure. If G6PD levels for the infant are unavailable, or if the infant is premature or G6PD-deficient, breastfeeding is not recommended unless long term serial laboratory monitoring of the infant's blood parameters can be performed.

Females and Males of Reproductive Potential

Animal studies demonstrated "slight" changes in viable fetuses (decreased by 15% per PT reviewer) but these were seen in the context of maternal toxicity and are unlikely to be relevant to humans. There are no human data regarding the effect of tafenoquine on fertility.

Because of concerns about embryofetal toxicity due to a G6PD-deficiency in the fetus, DPMH is recommending pregnancy testing prior to administration for section 8.3. Contraception for women during treatment is recommended for the same reason.

LABELING RECOMMENDATIONS

DPMH revised the HPI, sections 4, 5, 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on May 8, 2018. DPMH recommendations are below and reflect the discussions with DAIP. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Krintafel (tafenoquine) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------CONTRAINDICATIONS----------

- Breastfeeding by a lactating woman when her infant is found to be G6PD deficient (5.x, 8.2)

----------WARNINGS AND PRECAUTIONS----------

•Embryo-fetal Toxicity: KRINTAFEL may cause fetal harm when administered to a pregnant woman with a G6PD-deficient fetus. Advise of the potential risk to a fetus. (5.X, 8 1).

----------USE IN SPECIFIC POPULATIONS----------

- Lactation*:* Advise not to breastfeed a G6PD-deficient infant (4, 5.x, 8.2).

FULL PRESCRIBING INFORMATION

4 Contraindications

Reference ID: 4266131

Breastfeeding by a lactating woman when her infant is found to be G6PD deficient [*see Warnings and Precautions (5.x) and Use in Specific Populations (8.2)]*.

WARNINGS AND PRECAUTIONS

5.X G6PD Deficiency

Potential Harm to the Fetus

The use of Krintafel during pregnancy may cause hemolytic anemia in a fetus who is G6PD deficient. Even if a pregnant woman has normal levels of G6PD, the fetus may have deficient levels of G6PD. Advise females of reproductive potential that KRINTEFAL treatment during pregnancy is not recommended because there are other drug options available to treat malaria and to use effective contraception during treatment with KRINTEFAL. If a pregnancy is detected during KRINTEFAL use, discontinue KRINTEFAL as soon as possible and switch to a preferred treatment for malaria during pregnancy [*see Use in Specific Populations (8.1 and 8.3)*].

Potential Harm to the Breastfeeding Infant

An infant with G6PD deficiency may be at risk for hemolytic anemia from KRINTEFAL exposure through breast milk. Infant G6PD levels should be checked before lactation begins. Advise the woman with an infant who has G6PD deficiency not to breastfeed during treatment with KRINTEFAL and for 3 months after the final dose *[see Contraindications (4), Use in Specific Populations (8.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The use of Krintefal during pregnancy may cause hemolytic anemia in a fetus who is G6PD deficient. KRINTEFAL treatment during pregnancy is not recommended because there are other drugs options available to treat malaria. If a pregnancy is detected, discontinue KRINTEFAL as soon as possible and switch to a preferred treatment for malaria during pregnancy *[see Warnings and Precautions (5.X)]*. Available data with KRINTAFEL use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal studies, there were increased abortions, with and without maternal toxicity when tafenoquine was given orally to pregnant rabbits at and above doses equivalent to about 0.4 times the clinical exposure based on body surface area comparisons.

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

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

Reference ID: 4266131

Data

Animal Data

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

8.2 Lactation

Risk Summary

A breastfed infant with G6PD deficiency is at risk for hemolytic anemia from KRINTAFEL exposure. Infant G6PD status should be checked before lactation begins. An infant with G6PD deficiency should not be breastfed during maternal use of KRINTEFAL *[see Contraindications (4) and Clinical Considerations]*. There is no information regarding the presence of KRINTAFEL in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. In a breastfed infant with normal G6PD, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KRINTAFEL and any potential effects on the breastfed infant from KRINTAFEL or from the underlying maternal condition.

Clinical Considerations

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status in females of reproductive potential prior to initiating treatment with KRINTAFEL. *[see Dosage and Administration (2.x), Warnings and Precautions, (5.x), and Use in Specific Populations (8.1)]*.

Contraception

KRINTEFAL may cause hemolytic anemia in a G6PD deficient fetus *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential that KRINTEFAL treatment during pregnancy is not recommended because there are other drug options available to treat malaria and to use effective contraception during treatment with KRINTEFAL. If a pregnancy is detected during KRINTEFAL use, discontinue KRINTEFAL as soon as possible and switch to a preferred treatment for malaria during pregnancy.

17 PATIENT COUNSELING INFORMATION

Reference ID: 4266131

Embryofetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.x) and Use in Specific Populations 8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with KRINTEFAL *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women with a G6PD-deficient infant not to breastfeed during treatment with KRINTAFEL and for 3 months after the final dose *[see Contraindication (4), Warnings and Precautions 5.x, Use in Specific Populations (8.2)]*.

Reference ID: 4266131

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANE E LIEDTKA
05/21/2018

MIRIAM C DINATALE
05/21/2018

LYNNE P YAO
05/21/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 7, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 210795
Product Name and Strength:	Krintafel (tafenoquine) Tablets, 150 mg
Applicant/Sponsor Name:	GlaxoSmithKline Intellectual Property Development, Ltd. England
FDA Received Date:	April 17, 2018
OSE RCM #:	2017-2403-1
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Anti-Infective Products (DAIP) requested that we review the revised conainer labels for Krintafel (tafenoquine) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels for Krintafel are acceptable from a medication error perspective. We have no further recommendations at this time.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Myers, D. Label and Labeling Review for Krintafel (NDA 210795). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 20. RCM No.: 2017-2403.

Reference ID: 4259063

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEBORAH E MYERS
05/07/2018

OTTO L TOWNSEND
05/07/2018

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA210795
Brand Name	Krintefal
Generic Name	Tafenoquine
Sponsor	GlaxoSmithKline Intellectual Property Development Ltd. England
Indication	Radical cure (prevention of relapse) of P. vivax malaria in adults and adolescents 16 years and older
Dosage Form	Hard gelatin capsule administered orally
Drug Class	Synthetic analogue of primaquine
Therapeutic Dosing Regimen	Single 300 mg dose
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	600 mg single dose or 400 mg/d for 3 days or 600 mg/week for 10 weeks
Submission Number and Date	001, 11/22/2017
Review Division	DAIP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of tafenoquine was detected in the TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between tafenoquine at 3 different dose levels (300 mg single dose, 600 mg single dose and 1200 mg cumulative dose) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was less than 5 ms with the by-time analysis; however, we attributed this response to the lower than expected mean C_{max} for moxifloxacin observed in this study (1.5 µg/mL vs. 2.9 µg/mL reported in Florian J. *et al*., J Clin Pharm, 2011). Nevertheless, the slope of concentration-QTc relationship for moxifloxacin (3.5 ms per µg/mL) was similar to the expected slope of 3.1 ms per µg/mL, and overall time-profile for concentration and ΔΔQTcF was consistent with the expected time profile (Figure 3). Therefore, we concluded that assay sensitivity was demonstrated.

Reference ID: 4244730

In this randomized, single blinded, placebo-controlled, parallel-group study, approximately 52 subjects were enrolled in each treatment arm of five arms. Fifty two healthy subjects in each treatment arm received tafenoquine 300 mg, 600 mg, and 1200 mg, placebo and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for tafenoquine (300 mg, 600 mg and 1200 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
TQ 300 mg single dose	72	1.7	(-1.8, 5.2)
TQ 600 mg single dose	48	2.7	(-0.8, 6.2)
TQ 1200 mg cumulative dose	72	6.3	(2.8, 9.9)
Moxifloxacin 400 mg*	4	8.0	(4.4, 11.6)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 3.2 ms. TQ= Tafenoquine.

The supratherapeutic dose (1200 mg) produced mean C_{max} values ~3.9-fold the therapeutic exposures with proposed dose (a single 300 mg dose administered with food) and ~2.8-fold the high exposure scenario (drug interaction with chloroquine which increases tafenoquine's C_{max} by 38%). There was no evidence of a concentration-QTc relationship.

2 PROPOSED LABEL

The Sponsor 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), tafenoquine did not prolong the QT interval to any clinically relevant extent.

The following is QT-IRT's proposed labeling language, which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of tafenoquine 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)

Reference ID: 4244730

3 BACKGROUND

3.1 PRODUCT INFORMATION

Tafenoquine is a synthetic analogue of primaquine and is an antimalarial indicated for the radical cure (prevention of relapse) of Plasmodium vivax malaria in patients aged 16 years of age and older. Tafenoquine is given as a single 300-mg dose (two 150-mg tablets) with food on the first or second day of chloroquine administration.

3.2 MARKET APPROVAL STATUS

Tafenoquine is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Effect on hERG: In an in vitro assay using human embryonic kidney 293 (HEK293) cells stably expressing hERG channels, tafenoquine (0.129, 0.410, 1.29 and 4.10 µM) inhibited hERG channel tail current in a concentration-dependent manner. The nominal IC_{50} value was estimated to be 1.1 µM (equivalent to 0.51 µg/mL).

Effect on action potential parameters in dog isolated Purkinje fibres: Tafenoquine, at concentrations of 1 or 10 µM, had no effect on upstroke amplitude (UA), maximum rate of depolarisation (MRD), resting membrane potential (RMP) and action potential duration (APD) at 60% or 90% depolarisation in isolated dog Purkinje fibres stimulated at 0.2 or 1 Hz. At 100 µM (1 Hz), there was a significant decrease (54%) in MRD, and a decrease in UA in 3 of 4 fibres tested (mean fall of 24.4 mV). Marked depolarisation of the RMP was evident in 2 of 4 fibres. RMP, UA and MRD were statistically significantly decreased at 0.2 Hz. These results suggest a possible block of sodium and potassium channels. APD was unaltered at 100 µM, although the impact of other changes on action potential morphology may have affected reliable measurement of this parameter. A positive control, *dl*-sotalol (selective for Ikr), gave the expected results.

Cardiovascular and pulmonary effects in anesthetised dogs: Single doses of 19, 42 or 65 mg/kg given intravenously over 20 minutes to anesthetised dogs (n=6/group) caused generally dose-related increases in respiration rate and minute volume, and a fall in heart rate after the end of the infusion period. Blood pressure was decreased, and stroke volume, pulmonary arterial and wedge pressures and cardiac output increased at ≥42 mg/kg. The changes were very similar to those induced by the structurally closely related primaquine, with the minimally effective dose of tafenoquine (18 mg/kg; 2.0 µmoles/kg/min) being slightly greater than the maximum tolerated dose of primaquine (1.75 µmoles/kg/min). These observations should be regarded with caution, because falling blood pressure during the course of vehicle treatment suggested poor maintenance of anaesthesia.

Cardiovascular effects in conscious dogs: Conscious dogs (n=4) given single oral doses of 0.5 or 16 mg/kg showed no changes in blood pressure, heart rate, electrocardiogram (ECG) amplitude or ECG intervals, including QRS complex duration and rate-compensated QT interval. Mean Cmax and AUC0-168 values at 16 mg/kg were 1.35 µg/mL and 116 µg.h/mL, respectively.

Source: Investigator's Brochure version 14 (12 December 2017), page 24

Reference ID: 4244730

3.4 PREVIOUS CLINICAL EXPERIENCE

The primary evidence for the clinical safety of tafenoquine 300 mg single dose for radical cure of P. vivax malaria is provided by 3 randomized, double-blind studies; TAF112582 Part 1 (Phase 2b), TAF112582 Part 2 (pivotal Phase 3), and TAF116564 (Phase 3). Per the Sponsor, in these studies, there were no subjects with clinically significant abnormal ECG findings in the tafenoquine+chloroquine group. Observed changes in QTcF were consistent with the known effects of chloroquine on QT prolongation with no evidence of a clinically significant additional effect on QTcF values in the tafenoquine+chloroquine group.

Source: Clinical Summary of Safety Section 4.2

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of tafenoquine's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 101471. The sponsor submitted the study report for tafenoquine, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Randomized, Placebo-Controlled Study to Evaluate the Effect of Tafenoquine (SB252263) on the Electrocardiogram (ECG) with Focus on Cardiac Repolarization (QTc duration) in Healthy Subjects.

4.2.2 Protocol Number

TAF114582

4.2.3 Study Dates

29 July 2011 to 04 June 2012

4.2.4 Objectives

Primary objective

To demonstrate a lack of effect of tafenoquine on QT duration corrected for heart rate by Fridericia's formula (QTcF) following a supratherapeutic dose 3 x 400 mg (i.e. 400 mg per day on three consecutive days) as determined by the baseline-adjusted, maximum time-matched QTcF effect as compared to placebo.

Secondary objectives

- To demonstrate a lack of effect of tafenoquine following single doses of 300 mg and 600 mg as determined by the baseline-adjusted, maximum time-matched QTcF effect as compared to placebo.

Reference ID: 4244730

- To estimate the effect of tafenoquine 300 mg and 600 mg single doses on QT duration corrected for heart rate by Bazett's formula (QTcB), Individual-based corrected QT interval (QTci), QT interval, and heart rate (HR) as compared to placebo.
- To estimate the effect of a supratherapeutic dose tafenoquine (total 1200 mg over 3 days) on QTcB, QTci, QT interval, and HR as compared to placebo.
- To estimate the effect of single doses moxifloxacin (400 mg) on QTcF, QTcB, QT interval, and HR compared to placebo.
- To describe the pharmacokinetics of tafenoquine.
- To describe the pharmacokinetics of moxifloxacin (if needed).
- To characterize any pharmacokinetic (PK)/pharmacodynamic (PD) relationship between concentrations of tafenoquine and changes in electrocardiogram (ECG) parameters (QTcF, QTcB, and QT interval), if ECG effects were observed.
- To evaluate the safety and tolerability of tafenoquine.

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, single-blind, placebo-controlled, parallel-group study to assess the changes in QT duration due to therapeutic and supratherapeutic dose of tafenoquine compared to placebo and moxifloxacin in eligible healthy subjects. Moxifloxacin served as an active positive control.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

This was a single-blind study. The subjects were blindfolded when administering the study treatment. This was necessary to maintain the single blind because, the placebo for moxifloxacin, though similar in size to moxifloxacin, was of a different color. Blindfolding the subjects during all three treatment administrations, helped maintain the single-blind as well as ensured consistency in the day to day study treatment administration procedures. Sites ensured that other subjects could not see the subject taking medication to ensure only study staff were aware of blinding.

Reference ID: 4244730

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Group	Day 1	Day 2[4]	Day 3
1	A[1]	A[1]	A[1]
2	B[2]	B[2]	B[2]
3	A[1]	A[1]	C[3]
4	A[1]	A[1]	D[4]
5	A[1]	A[1]	E[5]

1. Treatment A = placebo for tafenoquine (6 capsules) + placebo for moxifloxacin (1 tablet)
2. Treatment B = tafenoquine (400 mg, 4 capsules) + placebo for tafenoquine (2 capsules) + placebo for moxifloxacin (1 capsule); henceforward referred to as the 1200 mg dose.
3. Treatment C = Placebo for tafenoquine (6 capsules) + moxifloxacin (1 tablet)
4. Treatment D = tafenoquine (300 mg, 3 capsules) + placebo for Tafenoquine (3 capsules) + placebo for moxifloxacin (1 tablet)
5. Treatment E = tafenoquine (600 mg, 6 capsules) + placebo for moxifloxacin (1 capsule)

4.2.6.2 Sponsor's Justification for Doses

A supratherapeutic tafenoquine dose of 1200 mg administered as 400 mg daily for three consecutive days was selected. Two additional doses of tafenoquine were also used in this study; the 300 mg single dose and the 600 mg single dose, both were administered on Day 3. The dose selection was primarily based on two factors; the adverse event profile of tafenoquine and the goal to achieve exposure that was multiples of anticipated maximal therapeutic exposure. A supratherapeutic dose in the form of single 1200 mg was not feasible considering that single 1200 mg (and above) doses were associated with a number of subjects experiencing an increase in Methemoglobinemia above 10%; a known effect of tafenoquine that has been seen in studies across various development stages. Furthermore, although pharmacokinetics of tafenoquine are approximately linear over the dose range 36 mg to 600 mg and after multiple weekly dosing of 200 mg and 400 mg, multiple weekly dosing of 600 mg was not chosen as a supratherapeutic regimen as concentrations did not appreciably increase compared to the 400 mg dose likely due to the high incidence of vomiting and diarrhea in the 600 mg dose group.

The chosen supratherapeutic regimen of 400 mg once daily for three days was tested in Study 058 where 22/46 subjects reported increased methemoglobin levels. However, the subjects were asymptomatic, did not require treatment intervention, and levels returned to at or near baseline levels by the Day 21 assessment.

Given the above considerations, the 1200 mg dose for tafenoquine in this protocol was 400 mg administered on Days 1, 2, and 3.

Reviewer's Comment: *Acceptable. The Sponsor's supratherapeutic dose of 400 mg once daily for three days provides adequate exposure margin to cover the worst case scenario (DDI with chloroquine). Geometric mean (CV%) C_{max} values after the last dose on Day 3 were 724 (24.7) ng/mL with this supratherapeutic dose. This is 3.9-fold the C_{max} for the therapeutic dose (300 mg single dose) of 186 ng/mL when administered with food. Furthermore, these concentrations are above those for the predicted worst case scenario (DDI with chloroquine, which causes 38% increase in tafenoquine's C_{max}).*

Reference ID: 4244730

4.2.6.3 Instructions with Regard to Meals

Doses were administered with food. Meals were consumed and doses taken at the same time on each occasion.

Reviewer's Comment: *A 31% increase in C_{max} was observed when tafenoquine was coadministered with a high fat meal. In order to reach adequate therapeutic exposure, the QT-IRT team had recommended that tafenoquine be given with food in this study. Tafenoquine is indicated for administration with food.*

4.2.6.4 ECG and PK Assessments

ECG Assessment:

12-Lead Mortara ECG monitoring was initiated in the morning of Day -1, such that it occurred 24 hours prior to scheduled dose administration on Day 1, and continued until the morning of Day 6, approximately 72 hours post Day 3 dose of study treatment. Triplicate ECGs were extracted from the Holter monitor recordings by the central reader at the following timepoints: pre-dose on Days 1 and 2; Day 3: pre-dose, 1, 2, 3, 4, 5, 6, 9, 12, 15, 20, 24, 36, 48, and 72 hours post Day 3 dose.

PK Assessment:

PK sampling scheme: at pre-dose on Days 1 and 2; Day 3: pre-dose, 1, 2, 3, 4, 5, 6, 9, 12, 15, 20, 24, 36, 48, and 72 hours post Day 3 dose.

Reviewer's Comment*: The ECG/PK sampling schedule was adequate to cover effects near T_{max} (~12 [3-48] h) and any delayed effects up to 72 h post-dose.*

4.2.6.5 Baseline

Time-matched baseline (Day -1) was used in this study for the primary analysis.

4.2.7 ECG Collection

Digital ECGs were obtained from 12-lead continuous Holter monitoring (Mortara H12 plus, 1000 Hz). Subjects remained in a supine or semi-supine position for at least 30 minutes prior to the ECG acquisition time point (for baseline days as well as days on placebo or active drug). All ECGs were read blinded. The same cardiologist/vendor read all ECGs for the same subject.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Approximately 52 healthy subjects were enrolled in each of the five groups to ensure 42 evaluable subjects in each group completed the study. Each subject participated in the study for approximately 13 weeks i.e., 38 day screening period, 8-day in-house period, and four follow-up visits approximately 5, 10, 24, and 60 days after the last dose of study medication.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

Reference ID: 4244730

Repeated measures models were fitted for the change from time-matched baseline QT using subject as random effects. Time, treatment, centre, gender and time by treatment interaction as fixed effects. Time-matched baseline QT was included as a time-dependent covariate. All final statistical models were fitted used a spatial power covariance structure to account for the within-subject correlation between QT measurements over the 14 time points post final dose. The hypothesis test for lack of QT effect controlled the overall Type I error rate at 5%.

The supratherapeutic dose of TQ 1200 mg compared to placebo showed a maximum effect on QTcF elongation which was just within the safety margin of 10 msec set out in the FDA E14 guidelines for lack of effect (Table 29). The largest effect were observed at 36 hours post final dose (mean 6.39 msec, 90% CI: 2.86, 9.92) and at 72 hours post final dose (mean 6.39 msec, 90% CI: 2.85, 9.94).

The moxifloxacin-induced QTcF effect indicated a maximum mean treatment difference of 8.52 msec (90% CI 5.00, 12.04) compared to placebo at 4 hours post dose.

The secondary analysis comparing the clinical doses of TQ (300 mg and 600 mg) to placebo demonstrated a lack of effect on QTcF elongation for these dose levels.

Reference ID: 4244730

Table 2: Summary of Results of Repeated Measures Statistical Analysis of QTcF Change from Baseline in TAF114582 (PD Summary Population)

	Mean Treatment Effect (msec)					Treatment Difference (msec) Mean (90% Confidence Interval)			
Day 3	PBO	Moxi	TQ 300	TQ 600	TQ 1200	Moxi-PBO	TQ 300-PBO	TQ 600-PBO	TQ 1200-PBO
1 H	-2.33	-0.15	-3.63	-5.54	1.19	2.19 (-1.33, 5.70)	-1.29 (-4.85, 2.26)	-3.21 (-6.70, 0.29)	3.52 (-0.01, 7.05)
2 H	-4.09	2.31	-4.90	-4.39	0.72	6.40 (2.89, 9.92)	-0.81 (-4.37, 2.75)	-0.30 (-3.79, 3.18)	4.81 (1.29, 8.33)
3 H	-3.19	4.14	-4.57	-4.77	0.02	7.32 (3.81, 10.84)	-1.38 (-4.94, 2.18)	-1.58 (-5.06, 1.91)	3.20 (-0.32, 6.73)
4 H	-1.36	7.16	-2.55	-3.48	1.38	8.52 (5.00, 12.04)	-1.19 (-4.75, 2.37)	-2.11 (-5.61, 1.38)	2.75 (-0.78, 6.27)
5 H	0.72	8.37	-0.69	-2.41	2.86	7.64 (4.12, 11.16)	-1.41 (-4.98, 2.15)	-3.13 (-6.62, 0.35)	2.14 (-1.39, 5.66)
6 H	1.16	8.93	-0.92	-0.28	5.59	7.77 (4.25, 11.29)	-2.08 (-5.64, 1.47)	-1.44 (-4.93, 2.05)	4.43 (0.90, 7.95)
9 H	-1.63	4.88	-2.93	-2.13	3.13	6.50 (2.98, 10.03)	-1.30 (-4.86, 2.26)	-0.50 (-4.00, 2.99)	4.76 (1.23, 8.29)
12 H	-0.75	5.08	-0.50	0.41	3.93	5.83 (2.30, 9.36)	0.25 (-3.32, 3.82)	1.16 (-2.33, 4.66)	4.69 (1.16, 8.22)
15 H	3.49	9.26	1.44	3.90	8.75	5.77 (2.25, 9.30)	-2.04 (-5.62, 1.53)	0.42 (-3.08, 3.91)	5.26 (1.73, 8.79)
20 H	6.17	11.07	5.69	6.71	11.02	4.90 (1.38, 8.43)	-0.48 (-4.05, 3.10)	0.54 (-2.97, 4.04)	4.85 (1.31, 8.39)
24 H	1.73	4.92	2.25	2.40	5.40	3.20 (-0.33, 6.72)	0.52 (-3.05, 4.09)	0.67 (-2.82, 4.16)	3.67 (0.13, 7.21)
36 H	1.56	3.84	1.93	2.10	7.95	2.28 (-1.25, 5.81)	0.37 (-3.20, 3.94)	0.54 (-2.95, 4.04)	6.39 (2.86, 9.92)
48 H	1.16	3.95	1.11	3.69	5.69	2.79 (-0.74, 6.32)	-0.05 (-3.61, 3.52)	2.53 (-0.97, 6.02)	4.53 (0.99, 8.06)
72 H	1.74	2.05	2.59	1.85	8.13	0.31 (-3.22, 3.83)	0.85 (-2.71, 4.41)	0.10 (-3.39, 3.59)	6.39 (2.85, 9.94)

PBO=Placebo; Moxi=moxifloxacin

Source:TAF114582- Study Report, Table 29, page 79

Reviewer's Comments: *Supratherapeutic dose of TQ 1200 mg compared to placebo showed a maximum effect on QTcF elongation which is borderline (highest upper 90% CI of 9.9 ms) considering the safety margin of 10 msec set out in the FDA E14 guidelines for lack of effect. FDA independent analysis is in agreement with the sponsor's analysis (see Section 5.2).*

4.2.8.2.2 Assay Sensitivity

The lower bound of the 90% CI just reached 5 msec at 4 hours post dose (Table 3). As expected, the study also showed that the moxifloxacin-induced QT effect returned to baseline levels, with no significant treatment difference between moxifloxacin and placebo beyond 24 hours post dose.

Reference ID: 4244730

Table 3: Assay Sensitivity Analysis of Comparisons of Moxifloxacin vs Placebo in QTcF Change from Time-Matched Baseline

Day 3 Planned Time Point	Mean Treatment Effect		Mean Treatment Difference (SE)	90% Confidence Interval Moxi-PBO
	Moxi N=51	Placebo N=50		
1 H	-0.15	-2.33	2.19 (2.130)	-1.33, 5.70
2 H	2.31	-4.09	6.40 (2.130)	2.89, 9.92
3 H	4.14	-3.19	7.32 (2.129)	3.81, 10.84
4 H	7.16	-1.36	8.52 (2.134)	5.00, 12.04
5 H	8.37	0.72	7.64 (2.132)	4.12, 11.16
6 H	8.93	1.16	7.77 (2.132)	4.25, 11.29
9 H	4.88	-1.63	6.50 (2.138)	2.98, 10.03
12 H	5.08	-0.75	5.83 (2.141)	2.30, 9.36
15 H	9.26	3.49	5.77 (2.135)	2.25, 9.30
20 H	11.07	6.17	4.90 (2.136)	1.38, 8.43
24H	4.92	1.73	3.20 (2.139)	-0.33, 6.72
36 H	3.84	1.56	2.28 (2.142)	-1.25, 5.81
48 H	3.95	1.16	2.79 (2.140)	-0.74, 6.32
72 H	2.05	1.74	0.31 (2.136)	-3.22, 3.83

Source: TAF114582- Study Report, Table 31

Reviewer's Comments: *As described in sponsor's report, the largest lower bound was 5 ms without multiplicity adjustment and below 5 ms with multiplicity adjustment. FDA independent by-timepoint analysis presented in Section 5.2 also shows that the largest lower bound is less than 5 ms with and without multiplicity adjustment. The sponsor also conducted exposure-response analysis for moxifloxacin to justify that the assay sensitivity was appropriate (described in Section 4.2.8.4.2).*

4.2.8.2.3 Categorical Analysis

In the primary analysis population, 3/50 subjects in the placebo group, 9/50 subjects in the TQ 1200 mg group, 5/51 subjects in the moxifloxacin group, 6/48 subjects in the TQ 300 mg group, and 4/52 subjects in the 600 mg group had absolute QTcF, QTcB, or QTci > 450 msec at any time point during the study. Two subjects in TQ 1200 group had absolute QTci > 480 msec post baseline, one of whom had > 500 msec at multiple time points post final dose. There were no subjects who had a change in time-matched baseline QTcF or QTcB > 60 msec at any time point during the study.

Summary of frequency of maximum post-dose QTc Interval and maximum change from predose baseline is presented in the table below.

Reference ID: 4244730

Table 4: Summary of Frequency of Maximum Post-Dose QTc Interval (upper panel) and Maximum Change from Predose Baseline (ΔQTc; lower panel) (msec) in TAF114582

ECG Test	Category	Placebo (N=52)	Moxi (N=52)	TQ 300mg (N=52)	TQ 600mg (N=52)	TQ 1200mg (N=52)
QTcB	n	52	52	52	52	52
	0≤Value≤450	49 (94.2)	48 (92.3)	44 (84.6)	49 (94.2)	43 (82.7)
	450<Value≤480	3 (5.8)	4 (7.7)	8 (15.4)	3 (5.8)	8 (15.4)
	480<Value<500	0	0	0	0	1 (1.9)
	Value≥500	0	0	0	0	0
QTcF	n	52	52	52	52	52
	0≤Value≤450	52 (100.0)	51 (98.1)	51 (98.1)	52 (100.0)	50 (96.2)
	450<Value<=480	0	1 (1.9)	1 (1.9)	0	2 (3.8)
	480<Value<500	0	0	0	0	0
	Value≥500	0	0	0	0	0
QTcF	n	52	52	52	52	52
	Value≤30	50 (96.2)	50 (96.2)	47 (90.4)	49 (94.2)	46 (88.5)
	>30<Value≤60	2 (3.8)	1 (1.9)	5 (9.6)	3 (5.8)	6 (11.5)
	Value>60	0	1 (1.9)	0	0	0

Source: TAF114582- Study Report, Table 24-25

Reviewer's Comment: The sponsor's results in the table above are based on maximum value and predose baseline, which are slightly different from results from FDA independent analysis using average values and time-matched baseline. FDA independent analysis is presented in Section 5.2.

4.2.8.3 Safety Analysis

No deaths occurred during the study. A total of 6 subjects experienced SAEs, but none were related to QTc prolongation.

Two subjects experienced cardiac AEs.

- Subject (b) (6) (placebo) experienced mild palpitations on Day 6. The palpitations resolved after 4 hours and were not considered by the investigator to be related to the study drug. No Holter monitoring or paper ECG changes were noted.
- Subject (b) (6) (TQ 600 mg) experienced mild palpitations on Day 2. The palpitations resolved after 2 days and were considered by the investigator to be related to the study drug. This subject had sinus bradycardia on Days -1, 1, 3, and 4. This subject also had a 12-lead ECG abnormality on Day 2 that was not clinically significant and not described in the source data (Source Data: Table 10.26)

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results for tafenoquine are presented in Table 5. The mean C_{max} was 724 ng/mL following 1200 mg total dose (400 mg once daily for 3 days). C_{max} and AUC values in the thorough QT study were generally 3.9-fold higher following the third day administration of 400 mg tafenoquine for three days compared with single 300 mg

Reference ID: 4244730

tafenoquine when administered with food, the intended clinical dose. The mean tafenoquine plasma concentration-time profiles are illustrated in Figure 1.

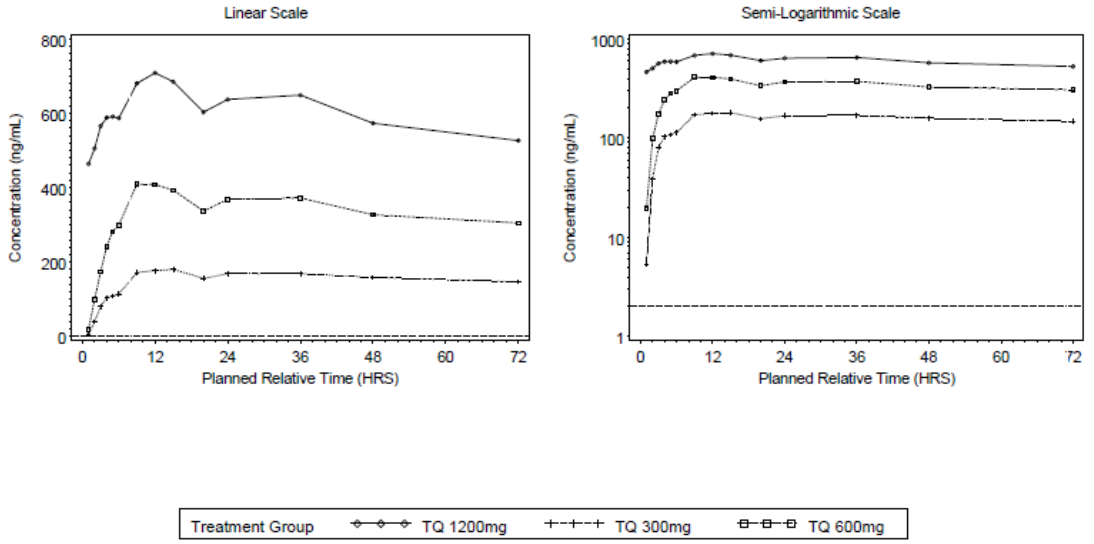
Table 5: Summary of Mean (CV%) Plasma Pharmacokinetic Parameters of Tafenoquine

Summary Plasma Tafenoquine Pharmacokinetic Parameters[1]					
Treatment	N	AUC(0-t) (ng·hr/mL)	Cmax (ng/mL)	tlast (hr)[2]	tmax (hr)[2]
300 mg Tafenoquine	51	10611 (29.7)	186 (31.3)	72.0 (71.9 - 73.0)	15.0 (8.98 - 48.2)
600 mg Tafenoquine	52	22986 (29.6)	422 (32.4)	72.0 (72.0 - 73.0)	12.0 (5.00 - 36.4)
1200 mg Tafenoquine	51	41896 (26.0)	724 (24.7)	72.0 (72.0 - 73.0)	12.0 (3.00 - 48.1)
1. Geometric Mean (CVb%)					
2. Median (range)					

tlast= time of last quantifiable concentration, CVb%=Within subject variability

Source: TAF114582- Study Report, Table 27, page 76

Figure 1: Mean Plasma Tafenoquine Concentration-Time Plots (Linear and Semi-Log) for 300 mg and 600 mg Single Tafenoquine Doses, and 400 mg Daily Dose for Three Days (1200 mg)



Source: TAF114582- Study Report, Figure 11.2, page 7191

4.2.8.4.2 Exposure-Response Analysis

The final E-R model included 2 cosine functions (an 8 hour cycle and a 24 hour cycle) and the covariates sex and race (2 groups) describing the baseline +placebo data and 2 slope terms, one for the tafenoquine concentrations vs QTcF, and the second for the moxifloxacin concentrations vs. QTcF. A bootstrap analysis was carried out which replicated the PK/PD

Reference ID: 4244730

parameters suggesting that the performance and stability of the model is acceptable (See Table 6 for model parameters).

Table 6: Comparison of Final Model Parameters and Bootstrap Results

		Final Model	Bootstrap Results	
Parameter	Units	Mean Estimate (%CV)[1]	Estimate	95% Confidence Interval
Baseline male white+	msec	399 (0.313)	399	(397,401)
Baseline female white+	msec	410 (17.8)	409	(404,415)
Baseline male black race	msec	391(22.0)	391	(388,396)
Baseline female black race	msec	401 (22.0)	401	(398,406)
Amp 8 hr	msec	4.18 (3.47)	4.18	(3.94,4.40)
tmax 8 hr	hr	-10.1 (0.385)	-10.1	(-10.2,-10.1)
Amp 24 hr	msec	3.99 (4.06)	4.00	(3.73, 4.28)
tmax 24 hr	hr	-4.46 (3.16)	-4.44	(-4.2,-4.7)
Slope Tafenoquine	msec/µg/mL	0.498 (175)	0.447	(-1.02,2.27)
Slope Moxifloxacin	msec/µg/mL	3.11 (17.0)	3.13	(2.27,4.00)
IIV (CV%) Baseline	msec	13.9 (8.03)	13.8	(12.9,14.7))
IIV (CV%) AMP 24 hr	msec	1.60 (26.0)	1.58	(1.19,1.90)
IIV (CV%) tmax 24 h	hr	1.22 (25.3)	1.22	(0.95,1.46)
IIV (CV%) AMP 8 hr	msec	0.906 (53.5)	0.90	(0.27,1.28)
IIV (CV%) tmax 8 hr	hr	0.43 (24.4)	0.974)	(0.34,0.51)
IIV (CV%) Moxi slope	msec/µg/mL	3.00 (30.2)	2.90	(2.20,3.70)
Random Residual Variability	msec	5.66 (2.75)	5.65	(5.58,5.78)

Source: TAF114582- Study Report, Table 41, page 104

Tafenoquine: Tafenoquine concentrations had only a small effect on change in QTcF interval (QTcF-TQ concentration slope of 0.498 msec/µg/mL). The bootstrap analysis did not show a statistically significant slope.

Moxifloxacin: The estimated slope for moxifloxacin (3.11 msec/µg/mL) is consistent with other thorough QT studies where moxifloxacin was considered a positive control [Garnett, 2008; Tornoe, 2011; Florian, 2011]. In this study, moxifloxacin was administered with food as previous moxifloxacin studies showed no substantial food effect [Florian, 2011]. However, the C_{max} and AUC values observed in this study were found to be approximately half that seen in studies in which moxifloxacin was administered under both fed and fasted conditions [Florian, 2011]. To examine the effect of higher concentrations of moxifloxacin, a dataset was created with all moxifloxacin concentrations doubled. Using this new dataset, 1000 studies were simulated in order to estimate ΔΔQTcF values at each of 7 selected time points between 0 and 6 hr post dose. Results of the simulations were used to determine the median predicted ΔΔQTcF for each study and median values of the medians from all studies plus the 90% CI at each time point which are shown in table below.

Reference ID: 4244730

Table 7: Median Predicted ΔΔQTcF and 90% Confidence Intervals for 2-Fold higher Moxifloxacin Concentrations

Time (hr)	Median Moxifoxacin Conc. (ng/mL)	Lower bound	Median ΔΔQTcF (msec)	Upper Bound
0	0	-1.67	-0.018	1.71
1	1072	1.19	3.43	6.07
2	2430	4.37	7.07	9.74
3	2730	5.47	8.22	11.06
4	2560	5.27	7.91	10.63
5	2340	4.66	7.25	9.67
6	2240	4.19	6.68	9.19

Source: TAF114582- Study Report, Table 42, page 106

The simulated data resulted in the lower bound of the 90% CI to be greater than 5.0 msec at 2 concentrations, 2730 ng/mL and 2530 ng/mL, at 3 and 4 h, respectively. These results show that the moxifloxacin effect on QTcF would have the expected effect on QTcF, had the concentrations of moxifloxacin been in the range of those observed in other studies where moxifloxacin was successfully used as the positive control. These results show that moxifloxacin can be considered a positive control in this study.

Reviewer's comments: *The reviewer's analysis is in agreement that there was no statistically significant positive slope for the concentration-QTc relationship for tafenoquine (see Section 5.3). The reviewer's analysis also confirmed that the slope of concentration-QTc for moxifloxacin was similar to the slopes reported in literature, supporting the acceptability of assay sensitivity (see Section 5.3).*

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

No large heart rate change (>10 bpm) were observed in the study (see Section 5.3). Therefore, QTcF was used for the primary statistical analysis and other analyses.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Tafenoquine

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment, center, sex, time, time and treatment as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables. The largest upper bounds of the 2-sided 90% CI for the mean difference between tafenoquine 300 mg and placebo, between tafenoquine

Reference ID: 4244730

600 mg and placebo and between tafenoquine 1200 mg and placebo were 5.2 ms, 6.2 ms, and 9.9 ms, respectively.

Table 8: Analysis Results of ΔQTcF and ΔΔQTcF for Tafenoquine

	Treatment Group									
	TQ 300mg				TQ 600mg			TQ 1200mg		
	Placebo	ΔQTcF	ΔΔQTcF		ΔQTcF	ΔΔQTcF		ΔQTcF	ΔΔQTcF	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	-1.4	-2.6	-1.1	(-4.7, 2.4)	-4.9	-3.5	(-7.0, 0.0)	1.1	2.5	(-1.0, 6.0)
2	-3.3	-3.9	-0.6	(-4.1, 3.0)	-3.7	-0.4	(-3.9, 3.1)	0.8	4.2	(0.7, 7.7)
3	-2.4	-3.5	-1.1	(-4.6, 2.4)	-4.1	-1.6	(-5.1, 1.8)	0.1	2.5	(-1.0, 6.1)
4	-0.5	-1.8	-1.2	(-4.7, 2.3)	-2.8	-2.3	(-5.8, 1.2)	1.4	2.0	(-1.5, 5.5)
5	1.7	0.3	-1.4	(-4.9, 2.2)	-1.7	-3.4	(-6.9, 0.1)	3.0	1.3	(-2.2, 4.8)
6	1.7	0.4	-1.3	(-4.8, 2.2)	0.4	-1.3	(-4.8, 2.1)	5.7	4.0	(0.5, 7.5)
9	-0.7	-1.6	-0.9	(-4.4, 2.6)	-1.4	-0.8	(-4.3, 2.7)	3.6	4.3	(0.8, 7.8)
12	0.2	0.6	0.4	(-3.1, 3.9)	1.1	0.9	(-2.6, 4.4)	4.0	3.8	(0.3, 7.3)
15	4.4	2.3	-2.1	(-5.6, 1.5)	4.6	0.2	(-3.3, 3.7)	8.8	4.4	(0.9, 7.9)
20	6.9	6.7	-0.2	(-3.7, 3.3)	7.4	0.5	(-3.0, 4.0)	11.2	4.3	(0.8, 7.8)
24	3.4	4.1	0.7	(-2.8, 4.3)	4.3	0.9	(-2.6, 4.4)	6.7	3.3	(-0.2, 6.8)
36	2.1	2.8	0.8	(-2.7, 4.3)	2.8	0.7	(-2.8, 4.2)	8.2	6.2	(2.6, 9.7)
48	2.9	3.4	0.5	(-3.0, 4.0)	5.6	2.7	(-0.8, 6.2)	7.0	4.1	(0.5, 7.6)
72	3.0	4.7	1.7	(-1.8, 5.2)	3.8	0.7	(-2.8, 4.2)	9.3	6.3	(2.8, 9.9)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9**.** The largest unadjusted 90% lower confidence interval is 4.5 ms. By considering Bonferroni multiplicity adjustment, the largest lower confidence interval is 3.2 ms, which indicates that a 5 ms QTcF effect due to moxifloxacin cannot be detected.

Table 9: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

Moxi					
	ΔQTcF	Placebo	ΔΔQTcF		
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	97.5% CI (ms)
1	0.1	-1.4	1.5	(-2.0, 5.0)	(-3.2, 6.3)
2	2.7	-3.3	6.0	(2.5, 9.5)	(1.2, 10.8)
3	4.4	-2.4	6.8	(3.3, 10.3)	(2.0, 11.6)
4	7.4	-0.5	8.0	(4.5, 11.5)	(3.2, 12.8)
5	8.7	1.7	7.0	(3.5, 10.5)	(2.2, 11.8)
6	9.2	1.7	7.5	(4.0, 11.0)	(2.7, 12.3)
9	5.3	-0.7	6.0	(2.5, 9.5)	(1.2, 10.8)
12	5.3	0.2	5.1	(1.6, 8.6)	(0.3, 9.9)
15	9.7	4.4	5.4	(1.9, 8.9)	(0.6, 10.2)
20	11.3	6.9	4.4	(0.9, 7.9)	(-0.4, 9.2)
24	6.8	3.4	3.4	(-0.1, 6.9)	(-1.4, 8.2)
36	4.3	2.1	2.2	(-1.3, 5.8)	(-2.6, 7.0)
48	5.6	2.9	2.7	(-0.9, 6.2)	(-2.2, 7.5)
72	3.7	3.0	0.7	(-2.9, 4.2)	(-4.1, 5.5)

* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

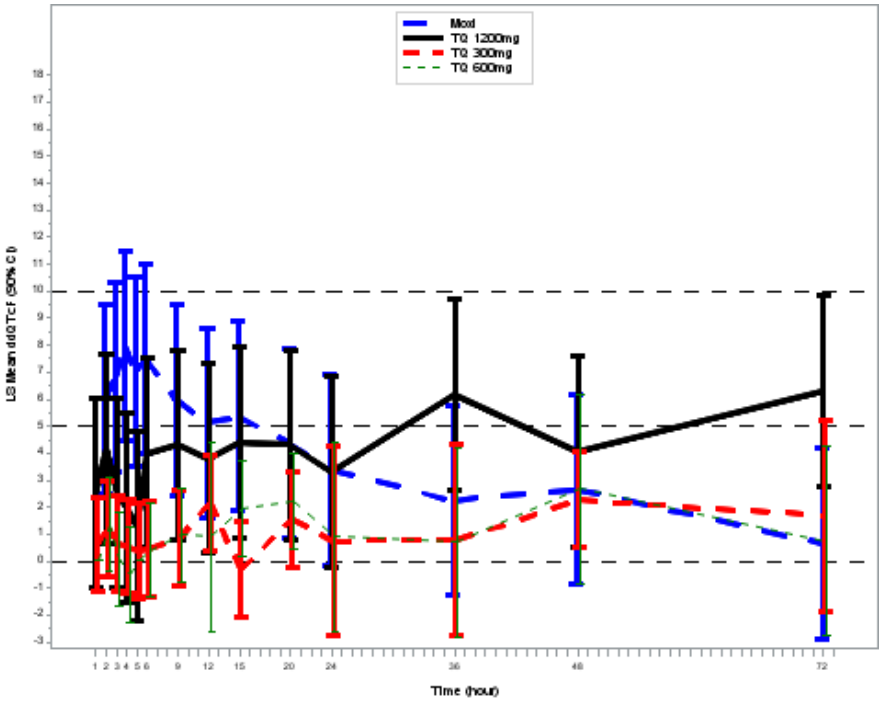
Reference ID: 4244730

Reviewer's comment: *The reviewer's concentration-QTc analysis for moxifloxacin for assay sensitivity is shown in Section 5.3.*

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 2: Mean and 90% CI ΔΔQTcF



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.4 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 10: Categorical Analysis for QTcF

	Total (N)		Value<=450 ms		450 ms<Value<=480 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Placebo	52	722	52 (100%)	722 (100%)	0 (0.0%)	0 (0.0%)
TQ 300 mg	51	711	51 (100%)	711 (100%)	0 (0.0%)	0 (0.0%)
TQ 600 mg	52	726	52 (100%)	726 (100%)	0 (0.0%)	0 (0.0%)
TQ 1200 mg	51	706	49 (96.1%)	704 (99.7%)	2 (3.9%)	2 (0.3%)

Reference ID: 4244730

Table 11 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 11: Categorical Analysis of ΔQTcF

	Total (N)		Value<=30 ms		30 ms<Value<=60 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Placebo	52	710	52 (100%)	710 (100%)	0 (0.0%)	0 (0.0%)
TQ 300 mg	51	708	51 (100%)	708 (100%)	0 (0.0%)	0 (0.0%)
TQ 600 mg	52	720	52 (100%)	720 (100%)	0 (0.0%)	0 (0.0%)
TQ 1200 mg	51	699	50 (98.0%)	698 (99.9%)	1 (2.0%)	1 (0.1%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the HR mean differences between tafenoquine 300 mg, tafenoquine 600 mg, and tafenoquine 1200 mg and placebo are 8.3 bpm, 6.7 bpm, and 5.7 bpm, respectively.

Table 12: Analysis Results of ΔHR and ΔΔHR for Tafenoquine (300 mg, 600 mg and 1200 mg)

	Treatment Group									
	TQ 300mg				TQ 600mg			TQ 1200mg		
	Placebo	ΔHR	ΔΔHR		ΔHR	ΔΔHR		ΔHR	ΔΔHR	
Time (hrs)	**LS Mean (bpm)**	**LS Mean (bpm)**	**Diff LS Mean (bpm)**	**90% CI (bpm)**	**LS Mean (bpm)**	**Diff LS Mean (bpm)**	**90% CI (bpm)**	**LS Mean (bpm)**	**Diff LS Mean (bpm)**	**90% CI (bpm)**
1	5.5	7.3	1.9	(-0.7, 4.5)	5.0	-0.4	(-3.0, 2.1)	5.9	0.4	(-2.1, 3.0)
2	2.2	4.4	2.3	(-0.3, 4.9)	3.4	1.3	(-1.3, 3.8)	3.6	1.4	(-1.1, 4.0)
3	-0.8	3.1	3.9	(1.3, 6.5)	2.0	2.8	(0.2, 5.4)	1.7	2.6	(-0.0, 5.1)
4	-1.4	2.0	3.4	(0.8, 6.0)	2.0	3.4	(0.9, 6.0)	1.7	3.1	(0.5, 5.7)
5	-1.6	2.8	4.3	(1.7, 6.9)	2.5	4.0	(1.5, 6.6)	0.7	2.3	(-0.3, 4.9)
6	-0.8	1.8	2.6	(0.1, 5.2)	3.4	4.2	(1.6, 6.7)	2.2	3.0	(0.4, 5.6)
9	3.0	7.5	4.4	(1.9, 7.0)	6.4	3.4	(0.8, 5.9)	5.8	2.8	(0.2, 5.4)
12	3.7	8.3	4.6	(2.0, 7.2)	6.4	2.7	(0.2, 5.3)	6.4	2.7	(0.1, 5.3)
15	2.6	5.5	3.0	(0.4, 5.5)	3.9	1.4	(-1.2, 3.9)	3.6	1.1	(-1.5, 3.6)
20	-2.3	2.5	4.8	(2.2, 7.4)	-1.1	1.2	(-1.4, 3.7)	0.5	2.8	(0.3, 5.4)
24	3.1	5.4	2.3	(-0.3, 4.9)	3.8	0.7	(-1.8, 3.3)	4.4	1.4	(-1.2, 4.0)
36	3.7	8.7	5.0	(2.4, 7.6)	6.0	2.3	(-0.3, 4.9)	6.9	3.1	(0.6, 5.7)
48	3.4	6.4	3.0	(0.4, 5.6)	4.3	0.9	(-1.7, 3.5)	4.4	1.0	(-1.6, 3.6)
72	4.9	10.7	5.7	(3.2, 8.3)	7.2	2.2	(-0.3, 4.8)	7.4	2.5	(-0.1, 5.1)

The outlier analysis results for HR are presented in Table 13. Six subjects experienced HR greater than 100 bpm in TQ 300 mg (3 subjects), TQ 600 mg (1 subject) and TQ 1200 mg (2 subjects) groups.

Table 13: Categorical Analysis of HR

	Total (N)	Value<=100 bpm	Value>100 bpm

Reference ID: 4244730

Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Placebo	52	727	52 (100%)	727 (100%)	0 (0.0%)	0 (0.0%)
TQ 300 mg	51	714	48 (94.1%)	710 (99.4%)	3 (5.9%)	4 (0.6%)
TQ 600 mg	52	728	51 (98.1%)	725 (99.6%)	1 (1.9%)	3 (0.4%)
TQ 1200 mg	51	712	49 (96.1%)	709 (99.6%)	2 (3.9%)	3 (0.4%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 14. The largest upper limits of 90% CI for the PR mean differences between tafenoquine 300 mg, tafenoquine 600 mg, and tafenoquine 1200 mg and the placebo are 8.3 ms, 8.8 ms, and 6.7 ms, respectively.

Table 14: Analysis Results of ΔPR and ΔΔPR for Tafenoquine (300 mg, 600 mg and 1200 mg)

	Treatment Group									
	TQ 300mg				TQ 600mg			TQ 1200mg		
	Placebo	ΔPR	ΔΔPR		ΔPR	ΔΔPR		ΔPR	ΔΔPR	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	-3.6	-1.0	2.6	(-2.1, 7.3)	0.5	4.1	(-0.6, 8.8)	-1.6	2.0	(-2.7, 6.7)
2	-1.7	-1.1	0.6	(-4.1, 5.3)	-0.3	1.4	(-3.3, 6.1)	-2.7	-1.0	(-5.7, 3.7)
3	-2.3	-0.1	2.3	(-2.4, 7.0)	-1.2	1.1	(-3.6, 5.7)	-2.3	0.0	(-4.7, 4.7)
4	-1.2	0.2	1.4	(-3.3, 6.1)	0.2	1.4	(-3.3, 6.1)	-0.5	0.7	(-4.0, 5.4)
5	-0.8	1.8	2.6	(-2.1, 7.3)	-0.6	0.1	(-4.5, 4.8)	-1.2	-0.4	(-5.1, 4.2)
6	-1.0	2.0	3.0	(-1.7, 7.7)	0.1	1.1	(-3.5, 5.8)	-1.3	-0.3	(-5.0, 4.4)
9	-3.5	-3.1	0.4	(-4.3, 5.1)	-2.0	1.5	(-3.2, 6.1)	-3.6	-0.1	(-4.8, 4.6)
12	-3.6	-4.9	-1.3	(-6.0, 3.4)	-1.6	2.0	(-2.7, 6.6)	-3.6	-0.1	(-4.8, 4.6)
15	-1.8	-1.1	0.7	(-4.0, 5.4)	-0.7	1.2	(-3.5, 5.8)	-2.3	-0.5	(-5.2, 4.2)
20	2.2	3.7	1.6	(-3.2, 6.3)	4.6	2.4	(-2.2, 7.1)	2.1	-0.1	(-4.8, 4.6)
24	0.9	4.0	3.1	(-1.6, 7.8)	4.3	3.4	(-1.3, 8.0)	1.0	0.1	(-4.6, 4.8)
36	-1.1	-1.4	-0.3	(-5.0, 4.4)	-2.4	-1.3	(-6.0, 3.4)	-2.7	-1.6	(-6.3, 3.1)
48	1.1	4.7	3.6	(-1.2, 8.3)	3.8	2.7	(-1.9, 7.4)	0.1	-1.0	(-5.7, 3.7)
72	-1.1	2.4	3.5	(-1.2, 8.2)	2.6	3.6	(-1.0, 8.3)	0.8	1.8	(-2.9, 6.5)

The outlier analysis results for PR are presented in Table 15. Fourteen subjects experienced PR interval greater than 200 ms in three treatment groups. Among those 14 subjects, 2 subjects experienced PR interval greater than 220 ms.

Table 15: Categorical Analysis for PR

	Total (N)		Value<=200 ms		200 ms<Value<=220 ms		Value>220 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Placebo	52	722	48 (92.3%)	709 (98.2%)	4 (7.7%)	13 (1.8%)	0 (0.0%)	0 (0.0%)
TQ 300 mg	51	711	45 (88.2%)	695 (97.7%)	6 (11.8%)	16 (2.3%)	0 (0.0%)	0 (0.0%)

Reference ID: 4244730

	Total (N)		Value<=200 ms		200 ms<Value<=220 ms		Value>220 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
TQ 600 mg	52	726	47 (90.4%)	691 (95.2%)	3 (5.8%)	26 (3.6%)	2 (3.8%)	9 (1.2%)
TQ 1200 mg	51	706	48 (94.1%)	700 (99.2%)	3 (5.9%)	6 (0.8%)	0 (0.0%)	0 (0.0%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 16. The largest upper limits of 90% CI for the QRS mean differences between tafenoquine 300 mg, tafenoquine 600 mg, and tafenoquine 1200 mg and placebo are -0.1 ms, 0.8 ms, and 0.9 ms, respectively.

Table 16: Analysis Results of ΔQRS and ΔΔQRS for Tafenoquine (300 mg, 600 mg & 1200 mg)

	Treatment Group											
	TQ 300mg				TQ 600mg				TQ 1200mg			
	Placebo	ΔQRS	ΔΔQRS		ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)		Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)		Diff LS Mean (ms)	90% CI (ms)
1	0.6	-2.3	-2.9	(-4.7, -1.1)	-1.2		-1.8	(-3.6, 0.1)	-0.8		-1.4	(-3.2, 0.5)
2	0.3	-1.9	-2.2	(-4.0, -0.4)	-1.3		-1.5	(-3.4, 0.3)	-1.0		-1.2	(-3.1, 0.6)
3	0.5	-1.9	-2.4	(-4.2, -0.5)	-1.1		-1.5	(-3.4, 0.3)	-0.9		-1.4	(-3.2, 0.5)
4	0.4	-2.1	-2.5	(-4.3, -0.6)	-1.0		-1.4	(-3.2, 0.4)	-0.6		-1.0	(-2.8, 0.9)
5	0.9	-1.7	-2.7	(-4.5, -0.8)	-1.3		-2.2	(-4.0, -0.4)	-0.6		-1.5	(-3.3, 0.3)
6	1.0	-2.0	-3.1	(-4.9, -1.2)	-0.9		-1.9	(-3.8, -0.1)	-1.0		-2.0	(-3.9, -0.2)
9	1.0	-2.3	-3.4	(-5.2, -1.5)	-1.2		-2.2	(-4.0, -0.4)	-0.5		-1.5	(-3.4, 0.3)
12	0.4	-2.2	-2.7	(-4.5, -0.8)	-1.3		-1.7	(-3.5, 0.2)	-1.1		-1.5	(-3.3, 0.4)
15	1.1	-1.9	-3.0	(-4.8, -1.1)	-0.5		-1.6	(-3.5, 0.2)	-0.0		-1.1	(-3.0, 0.7)
20	1.0	-1.7	-2.7	(-4.5, -0.8)	-0.7		-1.7	(-3.5, 0.2)	-0.4		-1.4	(-3.2, 0.5)
24	2.1	0.1	-2.0	(-3.9, -0.2)	1.2		-1.0	(-2.8, 0.8)	0.7		-1.5	(-3.3, 0.4)
36	0.8	-1.2	-1.9	(-3.8, -0.1)	-0.8		-1.5	(-3.4, 0.3)	-0.5		-1.3	(-3.1, 0.6)
48	2.4	-0.3	-2.7	(-4.5, -0.8)	0.8		-1.6	(-3.4, 0.2)	0.8		-1.6	(-3.5, 0.2)
72	2.2	-0.6	-2.8	(-4.6, -0.9)	0.5		-1.7	(-3.5, 0.2)	0.8		-1.4	(-3.2, 0.5)

The outlier analysis results for QRS are presented in Table 17. There were 2 subjects who experienced QRS interval greater than 110 ms in TQ 300 mg, and TQ 1200 mg groups.

Table 17: Categorical Analysis for QRS

	Total (N)		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Placebo	52	722	36 (69.2%)	566 (78.4%)	15 (28.8%)	152 (21.1%)	1 (1.9%)	4 (0.6%)
TQ 300 mg	51	711	43 (84.3%)	648 (91.1%)	7 (13.7%)	58 (8.2%)	1 (2.0%)	5 (0.7%)
TQ 600 mg	52	726	37 (71.2%)	594 (81.8%)	15 (28.8%)	132 (18.2%)	0 (0.0%)	0 (0.0%)
TQ 1200 mg	51	706	35 (68.6%)	563 (79.7%)	15 (29.4%)	138 (19.5%)	1 (2.0%)	5 (0.7%)

Reference ID: 4244730

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

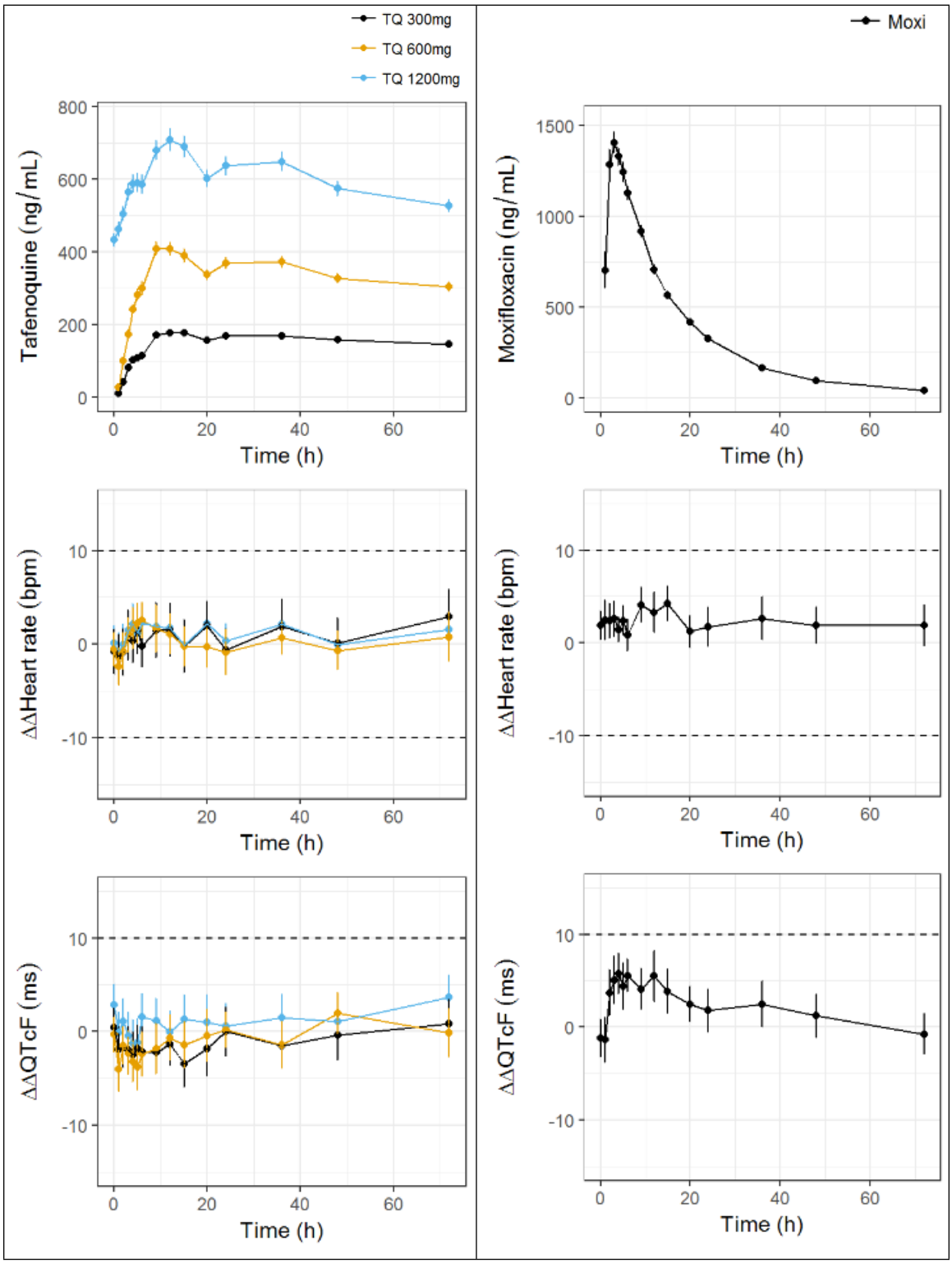
Figure 3 shows the comparison of drug concentration (tafenoquine and moxifloxacin), ΔΔQTcF and ΔΔHR for each of the sampling time points. The predose baseline was used in this representation.

For tafenoquine, there was no clinically relevant heart rate effect (increase or decrease by >10 bpm) and there was no systematic delay between PK and QTc effects. There was no dose-dependent relationship seen for ΔΔQTcF for tafenoquine (300 mg single dose, 600 mg single dose and 1200 mg [400 mg once daily for 3 days] cumulative dose).

For moxifloxacin, the overall time-profile for concentration and QTcF effects looked reasonable and consistent with the expected profile. However, the geometric mean C_{max} for moxifloxacin was 1.5 µg/mL, which is approximately half of the value of 2.9 µg/mL reported in the literature (Florian J. et al, J Clin Pharm, 2011;51:1152-1162). Administering moxifloxacin with food is not sufficient to explain the observed lower C_{max}. As per the above referenced manuscript, the food effect leads to ~27% decrease in oral absorption. Furthermore, there was no encapsulation of moxifloxacin in this study, which could have also resulted in lower C_{max}.

Reference ID: 4244730

Figure 3: Time-course of mean drug concentration (tafenoquine in left panel and moxifloxacin in right panel), ΔΔQTcF, and ΔΔHR

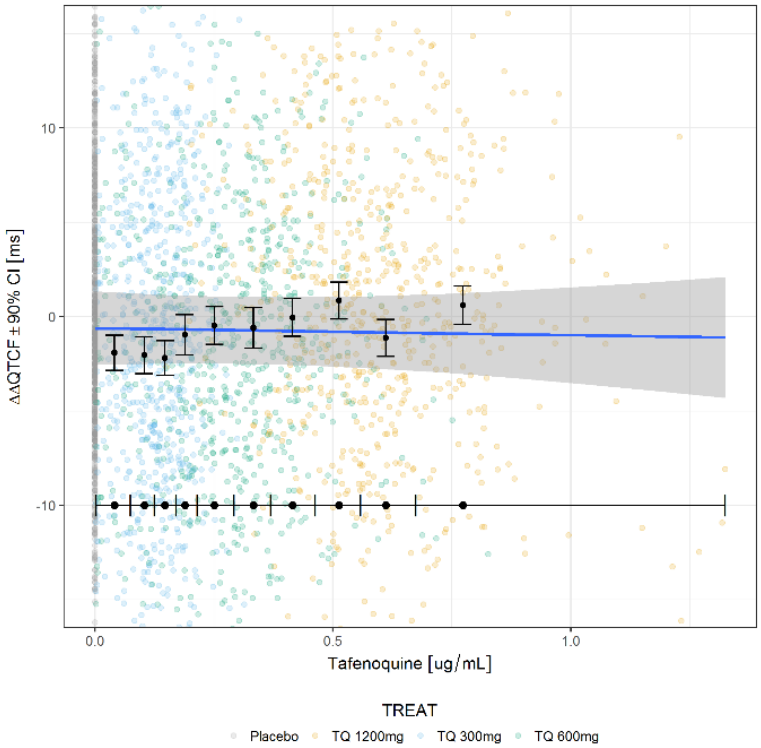


Reference ID: 4244730

Exposure-response for Tafenoquine

The concentration-QTc relationship was investigated using the recommended prespecified linear mixed-effects model. The predose baseline for QTcF was used in the analysis. The slope estimate from the model was -0.373 ms per µg/mL (p-value 0.8). The relationship between ΔΔQTcF and tafenoquine concentrations is visualized in Figure 4 with no evident exposure-response relationship. Mean predicted ΔΔQTcF at the tafenoquine C_{max} (735 ng/mL) for the supratherapeutic dose (400 mg once daily for three days; i.e., 1200 mg cumulative dose) is -0.9 ms with upper bound of 90% CI of 1.2 ms. This upper bound of 90% CI is well below the ICH E14 threshold of 10 ms.

Figure 4: ΔΔQTcF vs. Tafenoquine Concentrations



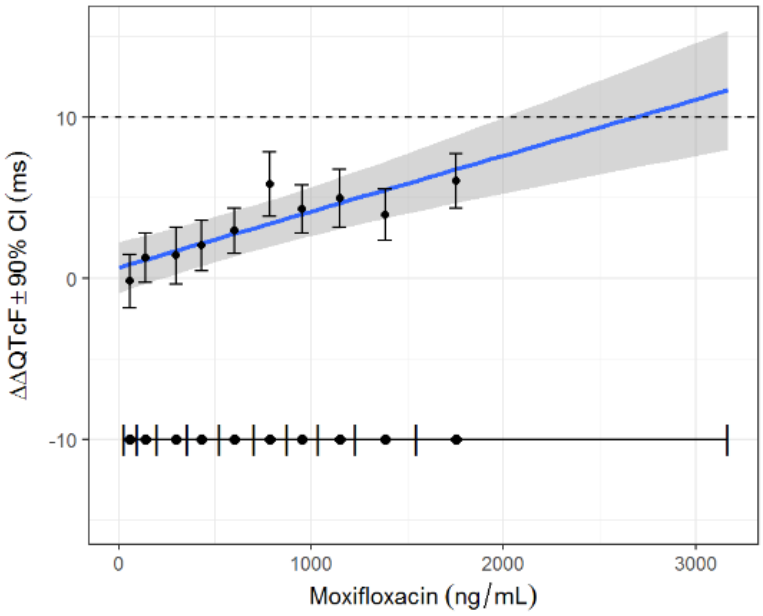
Exposure-response for Moxifloxacin

The concentration-QTc relationship was investigated using the recommended prespecified linear mixed-effects model. The predose baseline for QTcF was used in the analysis. There was a statistically significant positive relationship, with slope estimate from the model being 3.47 ms per µg/mL (p-value <0.001). The relationship between ΔΔQTcF and moxifloxacin concentrations is visualized in Figure 5. Mean (90% CI) predicted ΔΔQTcF at the C_{max} (1.5 µg/mL) for the 400 mg single dose of moxifloxacin in fed state, is 6.1 (4.1, 8.0) ms. The lower bound of 90% CI is below the threshold of 5 ms for assay sensitivity. Nevertheless, the slope of concentration-QTc relationship for moxifloxacin in this study (3.47 ms per µg/mL) was similar to the slope of 3.1 ms per µg/mL reported in literature (Florian J. et al, J Clin Pharm, 2011). Thus, the usual expected C_{max} of moxifloxacin (2.9 µg/mL) would certainly result in a lower bound of 90% CI >5 ms using the observed concentration-QTc relationship in this study. Furthermore, the overall time-profile for

Reference ID: 4244730

concentration and QTcF effects looked consistent with the expected profile supporting the acceptability of assay sensitivity for this study.

Figure 5: ΔΔQTcF vs. Moxifloxacin Concentrations



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

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 this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There are no clinically meaningful effects on the PR and QRS intervals.

Reference ID: 4244730

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	50-600mg single doses to be tested in Ph 2 dose ranging study in 2011	
Maximum tolerated dose	Maximum human single dose tolerated	600 mg
	Maximum human multiple dose tolerated (daily)	400 mg/d x 3d
	Maximum human multiple dose tolerated (weekly)	600 mg/week for 10 weeks
Principal adverse events	Most common adverse events	Nausea, vomiting, diarrhea, headache, abdominal pain & fatigue
	Dose limiting adverse events	Methemoglobinemia & diarrhea
Maximum dose tested	Single Dose	600 mg
	Multiple Dose	600 mg weekly for 10 weeks; 400 mg/d x 3 d
Exposures Achieved at Maximum Tested Dose	Single Dose (fasted) = 600 mg	Mean (%CV) Cmax: 273 (33.7%) ng/mL and AUC (0-t): 97.7 (26.1%) ug.h/mL
	Multiple Dose (fasted) = 600 mg weekly (See relative BA study below for 400mg/dx3d PK data)	Week 10 Mean (%CV) Cmax: 707 (22.5%) ng/mL and AUC(0-1 week): 78.3 (10.7%) ug.h/mL
Range of linear PK		36 - 600 mg single dose
Accumulation at steady state	Mean (%CV); specify dosing regimen	Approximately 3.2 to 4.4-fold based on 200 and 400 mg weekly dosing
Metabolites	Human	Unchanged tafenoquine is the only significant drug-related product detected in human plasma and blood, consistent with rat and dog. Excreted metabolites have not been tested for activity

Reference ID: 4244730

Absorption	Relative Bioavailability (Dose 400mg /d x 3 d, fed)	Mean Cmax and AUC (0-inf)(%CV): Formulation A. (Reference capsule): 758 (24.8%) ng/mL and 315 (21.6%) ug.h/mL; Formulation B. (new capsule): 741 (22.3%) ng/mL and 302 (25.5%) ug.h/mL; Formulation C. (tablet): 795 (36.9%) ng/mL and 330 (22.7%) ug.h/mL, respectively. 95% CIs were within standard BE acceptance range for all comparisons
	Tmax (Median, range) Parent	• Study 022 (200 mg SD) Fasted: 13 h (6-72 h); High fat meal: 14 h (5.6-144h) • Study 014 (400 mg/d x 3d)- Standard meal: Median (range) for parent: 12 h (4-36 h) on Day 3 of dosing
	Tmax (Median, range) Metabolites	• No major circulating metabolites identified-see above
Distribution	V2/F and V3/F	• V2/F: population mean 759 L (IIV 23%) and V3/F: 759 L (IIV not estimated) in healthy Caucasian subjects and Thai patients with *P. vivax* malaria (Study 058) • V2/F: population mean 1604 L (IIV 30.7%) in healthy Thai subjects and 1054 L (IIV 30.7%) in Thai patients with *P. vivax* malaria (Study 047). V3/F: Population mean 658.5 L (IIV(25.8%)for both healthy subjects and patients
	% bound	• => 99.5% for man
Elimination	Route of elimination	• Long elimination half-life precludes a human radiotracer study to quantify routes of elimination. Thus, the routes of elimination are not understood. However, metabolites detected in the urine were those previously seen in rats and/or dogs
		• Preclinical: Primary route via faeces: Rat 67%; Dog 35%; Monkey 56%, primarily as parent. Other routes - Biliary secretion: ~5% and 20% of oral dose in rat and dog, respectively, primarily as metabolites; urine 7%; 11%; 21% (rat, dog, monkey, respectively), primarily as metabolites. [Note: these numbers represent the minimum values as the long t½ was not well characterized when these studies were conducted]
	Terminal t½	• Healthy subjects - Range of means - 17.0-18.5 h (9.3-15.8%) (Study 014)

Reference ID: 4244730

	CL/F	• Population mean (%CV): 3.37 L/h (IIV 35.4%) in Thai subjects with *P. vivax* malaria and healthy Caucasian subjects (Study 058). • Population mean 2.77 L/h (IIV 23.6%) in healthy Thai subjects and Thai subjects with *P. vivax* malaria (Study 047)
Intrinsic Factors	Age	No effect of age (16-60 yr) observed on CL/F or V2/F. Further assessments to be conducted in Phase 3 study (Studies 047 & 058)
	Sex	No effect seen as covariate in study 022 & no effect observed in population PK analyses for studies 058 and 047
	Race	See V2/F and CL/F above
	Hepatic & Renal Impairment	No studies done
Extrinsic Factors	Drug interactions - effect of chloroquine on tafenoquine (Ratio (90% CI CQ+TQ:TQ alone)	Day 2 (first TQ dose): AUC (0-24): 1.24 (1.04, 1.46); Cmax 1.38 (1.17, 1.64). No other PK parameters were statistically significantly different (Day 3 PK, AUC (0-inf), t½)
	Drug interactions - effect of tafenoquine on other compounds	Desipramine CYP2D6 (study 015) - no statistically significant changes observed
		Flurbiprofen CYP2C9 (study 040) - no statistically significant changes observed
		Caffeine CYP1A2 (study 040) - no statistically significant changes observed
		Chloroquine/desethylchloroquine (study 491) - no statistically significant changes observed
	Food Effects	31% increase in Cmax & 41% increase in AUC(0-inf) with FDA high fat meal vs. fasted

Reference ID: 4244730

Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose	• There is a low risk that renal disease would influence the PK of tafenoquine, and a low risk of drug-drug interactions substantially affecting the PK of TQ. There is a potential risk for hepatic disease influencing the PK, however, based on the multiple Phase 1 and 2 type metabolites seen in the urine and bile of animals and in human urine, a large change in PK is unlikely. High fat meals increased the AUC (0-inf) and Cmax on average by 41% and 31%, respectively. From a safety perspective, 600 mg doses resulted in significant GI AEs (vomiting and diarrhea) in healthy subjects, whereas 400 mg doses did not. Hence, the supra-therapeutic dose selected is 1200 mg administered as 400 mg on Days 1, 3, and 4 • Based on the food effect and potential hepatic disease effect, an estimated two-fold increase in exposure can be considered a worst case scenario. Thus, the supra-dose selected for this study (total dose of 1200 mg) would cover the worst case increase in exposure for the highest potential dose to be investigated in the Phase 3 study

Reference ID: 4244730

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FERDOUSE BEGUM
04/05/2018

DALONG HUANG
04/05/2018

MOHAMMAD A RAHMAN
04/05/2018

DHANANJAY D MARATHE
04/05/2018

MICHAEL Y LI
04/05/2018

CHRISTINE E GARNETT
04/10/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 20, 2018
Requesting Office or Division:	Division of Anti-Infective Products
Application Type and Number:	NDA 210795
Product Name and Strength:	Krintafel (tafenoquine) Tablets, 150 mg
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	GlaxoSmithKline Intellectual Property Development, Ltd. England
Submission Date:	November 22, 2017
OSE RCM #:	2017-2403
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

Reference ID: 4237181

1 PURPOSE OF REVIEW VS REASON FOR REVIEW

As part of the approval process for Krintafel (Tafenoquine) Tablets, 150 mg, the Division of Anti-Infective Products (DAIP) requested that we review the proposed container label and prescribing information to identify areas of vulnerability that may lead to medication errors.

2 BACKGROUND MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

We note Krintafel is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency. We also note the container labels include the statement, "*Patients must be tested for glucose-6-phosphate dehydrogenase deficiency before taking this medicine*" in an orange highlighted box on the principal display panel. On March 13, 2018 we sent an Information Request (IR) to the Applicant asking that they provide their rationale for the inclusion of the statement "*Patients must be tested for glucose-6-phosphate dehydrogenase deficiency before taking this medicine*" in the orange highlighted box on the principal display panel (PDP) of the proposed container label.

In response to our March 13, 2018 IR, the Applicant states that, the primary safety liability for tafenoquine (and other 8-aminoquinolines) is drug-induced hemolysis in patients with Glucose-6-phosphate (G6PD) deficiency. Therefore, in addition to the inclusion of information regarding G6PD deficiency in the Contraindication, as well as in the Warnings and Precautions Sections of Prescribing Information, the Applicant's proposed packaging also highlights that pre-testing for G6PD deficiency is mandatory prior to use. Given that this product is intended to be administered as a single-dose treatment, the Applicant believes that the added precaution of including the need for testing on the packaging material itself might be warranted as an additional safeguard (full communication is available at the following link:

Reference ID: 4237181

\\cdsesub1\evsprod\nda210795\0015\m1\us\102-cover-letters\cover.pdf). We find the Applicant's rationale for inclusion of the warning regarding G6PD deficiency on the PDP of the proposed container label acceptable from a medication error perspective.

Tables 2 and 3 below include the identified medication error issues with the submitted container label and prescribing information, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Anti-Infective Products

Prescribing Information			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
General Issues			
1.	We note that the strengths include a hyphen between the number and mg (i.e., 300-mg and 150-mg) throughout the prescribing information (PI). This is inconsistent with other areas of the PI in which a hyphen is not present between the number and mg (e.g., 300 mg and 150 mg).	Inconsistent labeling may contribute to confusion that can result in medication error.	For consistency within the PI, we recommend removal of the hyphens between the number and mg (i.e., 300-mg and 150-mg) throughout the PI.
2.	In the Hightlights of Prescribing Information, *Dosage and Administration*, (b) (4) [redacted] the header, *Indications and Usage* of "…patients aged 16 years of age and older."	Inconsistent labeling may contribute to confusion that can result in medication error.	For consistency within the prescribing information, we (b) (4) [redacted] under Hightlights of Prescribing Information, *Dosage and Administration* to align with the age range under the header, *Indications and Usage* of "…patients aged 16 years of age and older."

Reference ID: 4237181

Highlights of Prescribing Information, *Dosage and Administration*			
1.	None		
Full Prescribing Information (FPI), Section 2, *Dosage and Administration*			
1.	We note that one of the strengths includes a hyphen between the number and mg (i.e., 150-mg). This is inconsistent with other areas of the prescribing information in which the hyphen is not present between the number and mg (e.g., 300 mg and 150 mg).	Inconsistent labeling may contribute to confusion that can result in medication error.	For consistency within the prescribing information, we recommend removal of the hyphen between the number and mg (150-mg). For example, "…administered as two 150 mg KRINTAFEL tablets…)
2.	The age range stated as (b) (4) [redacted] FPI, Section 1, *Indications and Usage* of "…patients aged 16 years of age and older."	Inconsistent labeling may contribute to confusion that can result in medication error.	For consistency within the prescribing information, we recommend changing the (b) (4) [redacted] ged 16 years and older)" to align with the age range in the FPI, Section 1, *Indications and Usage* of "…patients aged 16 years of age and older." For example, "…dose in patients aged 16 years of age and older is 300 mg administered…"
FPI, Section 3, *Dosage Forms and Strengths*			
1.	We note that the product strength includes a hyphen between the number	Inconsistent labeling may contribute to confusion that can result in medication error.	For consistency within the prescribing information, we recommend removal of the

Reference ID: 4237181

	and mg (i.e., 150-mg). This is inconsistent with other areas of the prescribing information in which the hyphen is not present between the number and mg (e.g., 300 mg and 150 mg).		hyphen between the number and mg (i.e., 150-mg). For example, "KRINTAFEL 150 mg tablets are…"
FPI, Section 16, *How Supplied/Storage and Handling*			
1.	The statement "Once opened, use within 3 months" is included on the 30-count container label. However, this information is not currently included in the FPI.	Specific information for appropriate dispensing of the drug product to maintain its identity, strength, quality, and purity should be included in the FPI.	To provide consistency with the information included on the container label, consider including the statement "Once opened, use within 3 months." under the bullet beginning with "Bottle of 30 tablets…"
2.	The listing for the "Bottle of 30 tablets" contains the notation, "child-resistant closure." However, the "Unit Dose Pack of 2 tablets" does not have this notation of a "child-resistant closure."	The information submitted by the Applicant under 3.2.P.7 *Container Closure System* in DARRTS indicates that the 2-tablets bottle also has a "child-resistant cap."	Add "child-resistant closure" to the "Unit Dose Pack of 2 tablets." For example, "Unit Dose Pack of 2 tablets in a bottle with child-resistant closure (NDC …"
3.	As currently presented the storage statement includes "Temperature excursions are permitted to 15° to 30°C (59° to 86°F)."	The units of temperature measurement following the first numbers in the temperature ranges (e.g., Centigrade symbol (C) following the 15° and Fahrenheit symbol (F) following the 59°) are missing.	Add the Centigrade symbol (C) following the 15° and Fahrenheit symbol (F) following the 59° within the storage information to provide clarity. For example, "Temperature excursions are permitted to 15°C to 30°C (59°F to 86°F)."

Reference ID: 4237181

Table 3: Identified Issues and Recommendations for GlaxoSmithKline Intellectual Property Development, Ltd. England (entire table to be conveyed to Applicant)

Container Labels (both 2-count and 30-count)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	As currently presented, the numerical part of the net quantity statements (2 and 30) appears more prominent than the proprietary name and the statement of strength (150 mg).	The proprietary name should be the most prominent information on the container label. Also, the product strength is considered to be "critical information."[a] To avoid strength confusion, the product strength statement should be prominently displayed on the principal display panel (PDP). Additionally, the net quantity statement should appear on the PDP, but should be separated from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded).[b]	We note there is no numeric overlap between the proposed strength and quantity; however, other strengths or quantities could be introduced in the future. Therefore, we recommend you decrease the prominence of the net quantity statements by relocating the numerical part of the net quantity statements (2 and 30) next to and in the same font type and height as the word "Tablets" of the net quantity statement. If your goal is to provide differentiation between the 2 and 30 count bottles you may consider the use of color coding techniques that are not more prominent than the statement of strength or proprietary name.
Container Label (30-count)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**

[a] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 134-151). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 461-463). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Reference ID: 4237181

1.	Currently the statement "Once opened, use within 3 months." appears in bold font on the side panel of the label.	Once the bottle is opened, the unused contents must be discarded after 3 months. If the user misses the discard information, it could result in the dispensing or administration of deteriorated product.	To increase the prominence of the discard information, we recommend including a space for healthcare providers to add the date that the product should be discarded. To assist with the calculation of the discard date, we recommend the inclusion of the reminder that the contents should be discarded 3 months after opening. In addition, we recommend changing the color of the font, surrounding this information with a box, and/or highlighting the information to draw attention to this important information (see example below): **Discard after ___/___/___.** **Discard unused portion 3 months after first opening.**

4 CONCLUSION

DMEPA's evaluation of the proposed container label and prescribing information identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division conveys Table 3 in its entirety to GlaxoSmithKline Intellectual Property Development, Ltd. England so that our recommendations are implemented prior to approval of this NDA.

Reference ID: 4237181

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Krintafel that GlaxoSmithKline Intellectual Property Development, Ltd. England submitted on November 22, 2018.

Table 4. Relevant Product Information for Krintafel	
Initial Approval Date	N/A
Active Ingredient	tafenoquine
Indication	Prevention of relapse of Plasmodium vivax malaria in patients aged 16 years and older.
Route of Administration	oral
Dosage Form	tablet
Strength	150 mg
Dose and Frequency	All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing Krintafel. Adults and adolescents (aged 16 years or older) are given Krintafel as a single 300-mg dose (two 150 mg tablets). Coadminister Krintafel on the first or second day of chloroquine administration. Krintafel should be taken with food to increase systemic absorption and minimize gastrointestinal side effects.
How Supplied	Bottle of 30 tablets with child-resistant closure Unit Dose Pack of 2 tablets in a bottle
Storage	Store at 20°C to 25°C (68°F to 77°F). Temperature excursions are permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Store in the original package to protect from moisture. Keep the bottle tightly closed and do not remove the desiccant.
Container Closure	Bottle of 30 tablets has a child-resistant closure.

Reference ID: 4237181

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 28, 2018, we searched the L:drive and AIMS using the terms, Krintafel and tafenoquine to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified four previous reviews[c,d,e,f], that we reviewed and determined that none were not applicable to this review.

[c] Sheppard, J. Proprietary Name Review for Krintafel (tafenoquine) IND 101471. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 FEB 02. RCM No.: 2014-44155.

[d] Myers, D. Proprietary Name Review for Krintafel (tafenoquine) NDA 210795. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 22. RCM No.: 2017-19475316.

[e] Myers, D. Proprietary Name Review for Kodatef (tafenoquine) IND 129656. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 25. RCM No.:2017-16434568.

[f] Myers, D. Proprietary Name Review for Terakoda (tafenoquine) NDA 210607. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2018 FEB 22. RCM No.:2017-19748803.

Reference ID: 4237181

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Krintafel labels and labeling submitted by GlaxoSmithKline Intellectual Property Development, Ltd. England on November 22, 2017.

- Container labels
- Prescribing Information (including detachable Patient Information) – available at the following link: \\cdsesub1\evsprod\nda210795\0000\m1\us\114-labeling\1141-draft\draft-clean.doc

F.2 Label and Labeling Images

- Container Label: Unit Dose Pack of 2 tablets in a bottle of 2 tablets (not to scale)

(b) (4)

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 4237181

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEBORAH E MYERS
03/20/2018

OTTO L TOWNSEND
03/20/2018