Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Tafenoquine succinate

Proprietary Product Name: Kodatef

Sponsor: Biocelect Pty Ltd

Date of first round report: 15 January 2018
Date of second round report: 13 March 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ACR	Adequate Clinical Response
ADF	Australian defence force
AE	Adverse event
BID	Twice a day
CI	Confidence intervals
CL/F	Total clearance of the drug from plasma after oral administration
CRU	Clinical research unit
EOS	End of study
ETF	End of therapy failure
FCT	Fever Clearance Time
G6PDD	Glucose-6-phosphate dehydrogenase deficiency
GCT	Gametocyte clearance time
GORD	Gastro-oesophageal reflux disorder
Hb	Haemoglobin
HPLC	High performance liquid chromatography
IBSM	induced blood stage *malaria*
IDMC	Independent Data Monitoring Committee
ITT	Intention to treat
MHb	Methaemoglobinaemia
N/A	Not applicable
NAMRU-2	Naval Medical Research Unit-2
OD	Once a day
Pf	Plasmodium falciparum
Pk	Plasmodium knowlesi

Abbreviation	Meaning
Pm	Plasmodium malariae
Po	Plasmodium ovale
Pv	Plasmodium vivax
PCT	Parasite clearance time
PK	Pharmacokinetics
PD	Pharmacodynamics
PE	Primary efficacy
PP	Per protocol
qPCR	Quantitative Polymerase Chain Reaction
SD	Standard deviation
USAMRU-K	USA Medical Research Unit Kenya
V/F	Volume of distribution
%CV	Coefficient of variation

1. Introduction

1.1. Submission identifying information

Submission number	PM-2017-02418-1-2
Sponsor	Biocelect Pty Ltd
Trade name	Kodatef
Active substance	Tafenoquine succinate

This is a Type A application to register a new chemical entity.

1.2. Drug class and therapeutic indication

Tafenoquine is a primaquine congener synthesised by adding a methoxy group at the 2 position, a methyl group at the 4 position, and a 3-trifluoromethylphenoxy substitution at the 5 position of the quinoline ring.

Tafenoquine succinate 125 mg tablet (containing 100 mg of free base) is indicated for a prophylaxis indication: '*Prevention of malaria in adults for up to 6 months of continuous dosing*'. The indication includes all species of Plasmodia and includes prophylaxis both in the endemic region and post-exposure ('post-exposure prophylaxis').

1.3. Dosage forms and strengths

Tafenoquine is presented as a dark pink, capsule shaped, film coated tablet containing 125.5 mg of tafenoquine succinate equivalent to 100 mg of free base.

1.4. Dosage and administration

The recommended preventative regimen for tafenoquine oral tablet is a loading dose of 2 x 100 mg tablets once daily for 3 days prior to travel to a malarious area, followed by weekly 2 x 100 mg maintenance doses while in the malarious area, followed by one dose of 2x100 mg in the week following exit from the malarious area.

Tafenoquine oral 100 mg tablets can be taken with or without food although tafenoquine taken with food may be associated with better gastrointestinal tolerance.

1.5. Proposed changes to the product documentation

This is a new PI for first time registration of a new clinical entity.

1. Background

1.1. Information on the condition being treated

Malaria is a potentially fatal illness caused by protozoal infection of red blood cells (RBC) with parasites belonging to the genus *Plasmodium*, transmitted to humans by the bite of a *Plasmodium* infected female *Anopheline* mosquito, usually between dusk and dawn. Five species

of *Plasmodium* (P) infect humans, namely, *P. falciparum* (Pf), *P. vivax* (Pv), *P. ovale* (Po), *P. malariae* (Pm), and *P. knowlesi* (Pk).

In 2015, an estimated 212 million cases of malaria occurred worldwide. 90% of the cases were due to infection with Pf in the WHO African Region; 7% were in the South-East Asia Region and 2% were in the Eastern Mediterranean Region. The huge number of Pf cases in sub Saharan Africa means that only about 4% of cases globally are caused by Pv, but outside the African continent the proportion of Pv increases to 41%. Of the total of 14,400,000 cases in the South-East Asia Region, 4,900,000 were due to Pv. For the Eastern Mediterranean Region, total cases were 3,800,000 and Pv cases were 1,400,000. For the Americas, total cases were 800,000 with Pv comprising a majority (500,000).

In 2015, an estimated 429,000 deaths from malaria occurred. Most deaths were estimated to have occurred in the African Region (92%), followed by the South-East Asia Region (6%) and the Eastern Mediterranean Region (2%). Although almost all deaths (99%) resulted from Pf malaria in Africa, Pv is estimated to have been responsible for 3100 deaths with most (86%) occurring outside Africa.[1]

1.2. Current treatment options

Malaria chemoprophylactic recommendations for regions where chloroquine-resistant Pf exists are atovaquone-proguanil, doxycycline and mefloquine. The duration of dosing after leaving the endemic region is based on whether the agent kills the initial liver stage of the parasite (a causal agent) in which case the duration is 7 days, or kills the subsequent blood stage of the parasite (a blood schizonticidal agent) in which case the duration is 28 days.

Atovaquone/proguanil (Malarone) prophylaxis should begin 1 to 2 days before travel to malarious areas and should be taken daily, at the same time each day, while in the malarious areas and, since this agent is causally-active, daily for 7 days after leaving the area.[2] Malarone prophylactic efficacy is approximately 98%. Adverse effects reported in persons using atovaquone/proguanil for prophylaxis or treatment includes abdominal pain, nausea, vomiting, and headache.

Doxycycline prophylaxis should begin 1 to 2 days before travel to malarious areas. It should be continued once a day, at the same time each day, during travel in malarious areas and daily for 4 weeks after the traveller leaves such areas. Efficacy is thought to be between 92 to 96%.[3] Doxycycline frequently causes mild-moderate nausea, vomiting, abdominal pain, photosensitivity, and vaginitis; and uncommonly can cause the severe reactions of esophagitis and oesophageal ulceration.

Mefloquine prophylaxis should begin 1 to 2 weeks before travel to malarious areas. It should be continued once a week, on the same day of the week, during travel in malarious areas and for 4 weeks after a traveller leaves such areas. Mefloquine prophylactic efficacy is approximately the same as that of Malarone. Mefloquine resistance, where present, will diminish that efficacy rate. Mefloquine has been associated with rare serious adverse reactions (for example, psychoses or seizures) at prophylactic doses; these reactions are more frequent with the higher doses used for treatment. Other side effects that have occurred in chemoprophylaxis studies include gastrointestinal disturbance, headache, insomnia, abnormal dreams, visual disturbances, depression, anxiety disorder, and dizziness. Other more severe neuropsychiatric disorders occasionally reported during post marketing surveillance include sensory and motor neuropathies (including paraesthesia, tremor, and ataxia), agitation or restlessness, mood changes, panic attacks, forgetfulness, confusion, hallucinations, aggression, paranoia, and encephalopathy. Psychiatric symptoms have been reported to continue long after mefloquine has been stopped. Mefloquine is contraindicated for use by travellers with a known hypersensitivity to mefloquine or related compounds (for example, quinine and quinidine) and in persons with active or a history of major psychiatric disorders, or seizures. It should be used

with caution in persons with psychiatric disturbances or a previous history of depression. Mefloquine is not recommended for persons with cardiac conduction abnormalities.

These drugs are all registered and available in Australia for malaria prophylaxis.

1.3. Clinical rationale

The wide range of side effects with both doxycycline and mefloquine, as well adherence to dosing regimens and prescribed chemoprophylaxis after leaving the country of exposure, are the major issues with these drugs being used effectively. Daily administration of drugs is a problem in relation to compliance (doxycycline and malarone). There is better adherence with weekly regimens (such as mefloquine), but the neuropsychiatric adverse effects of mefloquine have drastically curtained its use as a chemoprophylactic agent.

The unmet medical need for malaria chemoprophylaxis while in endemic regions is an effective, weekly drug without the neuropsychiatric adverse reactions of mefloquine.

In relation to post-exposure prophylaxis to kill Pv dormant forms (thus preventing relapse) the unmet medical need is a 1 dose regimen that will be inherently superior to 7 daily doses of Malarone, 4 weekly doses of Mefloquine, and either of those regimens combined with 14 daily doses of primaquine. Po malaria can also relapse, but is rarely seen in Australia.

1.4. Guidance

The major guidance comes from the FDA draft guidance on development of prophylactic antimalarial drugs[4] lists all of the following possible study designs. There are 3 alternatives for a pivotal trial, each with advantages and disadvantages:

1. A comparator controlled study can be performed in non-immunes. Historic placebo infection rates can be used to address this difficulty, and are required for a non-inferiority analysis of the study.
2. A placebo controlled study can be performed in a semi-immune population who, through repeated prior exposure to parasites, will tolerate infection well during the study. However, interpretation of the study data is difficult because of the unknown contribution of immunity to drug effect.
3. A placebo controlled study in non-immunes can be performed in the malaria challenge model in a clinical laboratory where subject safety is tightly monitored but the precise relevance of this model to parasite challenge in the real world is uncertain but protective efficacy can be shown.

It further states that prophylaxis applications can be significantly strengthened by studies involving treatment of established infection.

The submission includes the comparator controlled pivotal Study 033 (on military personnel stationed in Timor), supported by a placebo controlled prophylaxis study in semi-immunes in East Africa Study 045), and by a placebo controlled prophylactic study in non-immunes in a human challenge model (Study TQ-2016-02).

The primary efficacy endpoints and primary efficacy analytic endpoints are based the cumulative incidence of parasitemia, with incidence density (parasitology per unit time) being used for secondary analyses, in conformity with the FDA Guidance document.

1.5. Evaluator's commentary on the background information

The background information is adequate. The rationale for needing a prophylaxis medication that can be taken weekly and is free of neuropsychiatric side effects is good. The information about the global impact of malaria and the available prophylaxis in Australia is accurate. It would be relevant for the sponsor to provide information about the annual incidence of malaria in Australia.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The dossier documented a development program of pharmacology, dose finding, pivotal and other clinical trials.

Included in this dossier is data from 22 clinical trials, including eight Phase I pharmacokinetics (PK) and safety studies in healthy volunteers; 2 Phase I drug-drug interaction studies in healthy volunteers; 3 Phase I malaria challenge studies; 7 Phase II/III studies for malaria prophylaxis and 2 Phase II studies for the treatment of Pv malaria. These are summarised by phase in Tables 1 to 3 (Phase I) and Phase II/III (Table 4 and 5) along with the publications references. Table 6 summarises the submitted studies and designs, specifies the numbers in the cohorts and contains PK summary data.

The Phase II studies that support the key trials listed above consist of the following:

- Studies 053 and 054: Prophylactic efficacy of single dose (Study 053) and early multiple dose (Study 054) tafenoquine regimens in the human Pf challenge model.
- Study 006: Different loading doses for semi-immunes in Africa.
- Study 043: Different loading doses and 'full prophylactic regimens' (loading dose followed by weekly or monthly dosing) for semi-immunes in Africa.
- Study 044: 'Full prophylactic regimen' with a higher dose than the final clinical dose for non-immunes in South East Asia (Thailand)
- Study 030: The anticipated clinical regimen (200 mg per day x 3 days followed by200 mg weekly) compared to placebo and positive control (mefloquine).
- Study 049 compares tafenoquine to primaquine in non-immunes.
- Studies 047 and 058 compare tafenoquine to primaquine in Thai people with variable immunity.
- Study 046 enrolled only 1 subject and is not considered further.

For 'Prophylaxis of malaria after leaving the endemic region,' 5 relevant studies provide data.

- Study 033: Upon exit of non-immunes from the endemic region, mefloquine subjects received primaquine while tafenoquine subjects were not further treated (did not receive a post-exposure dose of tafenoquine, they received 14 days of placebo).
- Study 045: Prophylaxis in semi-immunes in East Africa.
- Study 047: Wide range of short tafenoquine regimens for Thai people in South East Asia
- Study 049: Several short tafenoquine regimens for Australian non-immunes
- Study 058: In addition to evaluating the treatment effect of tafenoquine against Pv already present in the blood of semi-immune Thai people, follow-up was extended to 120 days to assess relapse up to that time.

These can be summarised as:

- 14 studies providing PK, PD and safety pharmacology data.
- 1 one population PK data study
- 6 studies that use varying doses.
- 1 Population PK (popPK) analyses.
- 2 Pivotal efficacy/safety studies.
- 10 Other efficacy/safety studies.

A number of studies performed more than one function (having dose finding, efficacy and safety data).

Table 1: Phase I Studies in healthy volunteers

Study No.	Study Design (i)	Study Objectives	Tafenoquine Doses Administered	Population
Single Dose Studies				
050	R, DB, PC	PK and Safety in fasted state	4 -600mg	N=75; 75M/0F
052	R, PG	PK and Safety in fasted state	100, 200, or 400 mg	N=18; 18M/0F
003	R, O, PG	PK and Safety in fed vs fasted state. Gender effects.	400 mg	N=32;16M/16F
022	R, PG	PK and Safety in fed vs fasted state. Gender effects.	200 mg	N=40; 20M/20F
TQ-2016-01	O	Compare PK parameters of the new tafenoquine clinical formulation (100 mg tablets) to PK of the 200 mg capsule used in previous tafenoquine trials (specifically Study 022). Also, compare AEs, vital signs and hematology parameters.	200mg (dosed as two 100 mg tablets)	N=70
Multiple-Dose Studies				
051	R, DB, PC	PK and Safety in	200, 400, or 600	N=36; 30M/6F

Study No.	Study Design [(i)]	Study Objectives	Tafenoquine Doses Administered	Population
		fasted state	mg weekly x 10 weeks	
014	R, O, PG	Relative bioavailability of 3 different oral formulations.	400 mg daily x 3 days	N=58; 43M/15F
057	R, PC	Renal and ocular Safety.	200 mg daily x 3 days, then weekly x 23 weeks	N=120; 73M/47F

[(i)]R=Randomised; DB=Double-blind; P=Placebo-controlled trial; PG=Parallel-group; O=Open-label.

Table 2: Phase I Drug-Drug Interaction Studies in Healthy Volunteers

Study No.	Study Design[(i)]	Study Objectives	Tafenoquine Doses Administered	Population
015	O, SS	Study PK and DDI of tafenoquine+desipramine	400 mg daily x 3 days	34; 20M/14F
040	O, TP, NR, C	Study PK and DDI of tafenoquine+midazolam, flurbiprofen, caffeine	400 mg daily x 3 days	28; 18M/10F

[(i)]O=Open-label; SS=Single sequence; TP=Two-period; NR=Non-randomised; C=Crossover; DDI = Drug-drug interaction.

Table 3: Phase I Malaria Challenge Studies in Healthy Volunteers

Study No.	Study Design[(i)]	Study Objectives	Tafenoquine Doses Administered	Population
Single-Dose Studies				
053	R, DB, PC	Determine prophylactic efficacy of tafenoquine against Pf malaria in non-immune fasted subjects when given prior to mosquito inoculation	600 mg	N=6; 4M/2F
Multiple-Dose Studies				

Study No.	Study Design[i]	Study Objectives	Tafenoquine Doses Administered	Population
054	R, DB, PC	Determine whether tafenoquine was prophylactic against Pf malaria Gather PK (tafenoquine co-administered with food) and Safety data.	600 mg daily x 2 days, then 300 mg weekly x 4 weeks or 600 mg daily x 2 days, then 300 mg one week later	N=10; 10M/0F
TQ-2016-02	R, DB, PC	Evaluate the prophylactic activity of tafenoquine against challenge with Pf asexual blood stage parasites in non-immune participants; characterize the exposure-response relationship for tafenoquine; and provide safety and tolerability data for tafenoquine in a controlled disease-like setting.	200 mg daily x 3 days, then 200 mg one week later	N=16

[i]RCT=Randomised; DB=Double-blind; PC=Placebo-controlled. O=open label

Table 4: Malaria Prophylaxis Studies (Phase II and III)

Study No.	Study Design [i]	Study Objectives	Tafenoquine Doses Administered	Population
006	R, DB, PC	Malaria prevention in semi-immune subjects of Lamaréné, Gabon (highly endemic Pf)	25, 50, 100 or 200mg daily x 3 days	N=415; 194 M/221 F
030	R, DB, PC, AC (mefloquine)	Prevention of malaria in semi-immune subjects	200 daily x 3 days then 200 mg weekly for	N=300; 195 M/105 F

Study No.	Study Design (i)	Study Objectives	Tafenoquine Doses Administered	Population
		of Nyanza Province, Kenya (area holoendemic for Pf*)*	24 weeks	
033	R, DB, AC (mefloquine)	Prevention of malaria in non-immune members of the Australian Defense Force (ADF) deployed to Bobanaro District, Timor Leste (area mesoendemic for Pf and *Pv*)	200 mg daily x 3 days, then 200 mg weekly throughout deployment	N=654; 632 M/22 F
043	R, DB, PC, PG	Determine the chemosuppressive effectiveness of weekly regimens of tafenoquine in preventing falciparum parasitemia compared with placebo in semi-immune Kenyan subjects.	400 mg daily x 3days or 200 mg daily x 3days, then 200mg weekly for 10-15 weeks or 400 mg daily x 3days, then 400 mg weekly for 10-25 weeks	Tafenoquine groups 174; 109 M/ 65 F
044	R, DB, PC	Determine the efficacy of monthly doses of tafenoquine v. placebo in the chemoprophylaxis of multi-drug resistant Pf and *Pv* in Thailand.	400 mg daily x 3d, then 400 mg monthly	Tafenoquine n=104 Placebo n=101
049Post-exposure Prophylaxis	O, R, PG, AC (primaquine)	Compare the effectiveness and tolerability of tafenoquine with primaquine in preventing *Pv* malaria in non-immune ADF after leaving malarious areas of Papua New Guinea and	200 mg daily x 3 days or 200 mg twice daily x 3 days or 400 mg daily x 3 days	N=1512; 1431 M/ 81 F

Study No.	Study Design [i]	Study Objectives	Tafenoquine Doses Administered	Population
		East Timor.		

R=Randomised; DB=Double-blind; PC=Placebo Control; AC=Active Comparator; PG=Parallel Group; O=Open label

Table 5: Pv Treatment Studies (Phase II)

Study No.	Study Design [i]	Study Objectives	Tafenoquine Doses Administered	Population
047	R, O, NC (CQ)	Determine efficacy of various dosing regimens of tafenoquine when combined with chloroquine in preventing relapse of *Pv* malaria in Thailand. Safety and PK of tafenoquine in normal and infected subjects.	500 mg once or 500 mg x 3d, repeated 1 week later or 300 mg daily x 7d	N=79; 38M/41F
058	R, DB, AC,	Assess whether treatment with tafenoquine alone could radically cure *Pv* malaria in adults.	600 mg once or 400 mg daily x 3 days	N=120; 60M/60F

[i]R=Randomised; O=Open label; DB=Double blind; NC=Negative control; CQ=Chloroquine; AC=Active control.

Table 6: Summary of studies and design

Study No./ Phase	Study Type	Study Design	Doses	Sample Size	ka (1/h)	CL/F (L/h)	V/F (L)	t½ (h)	Cmax (ng/mL)	Tmax (hrs)	Cmin	AUC$_{tau}$ µg·h/mL	AUC$_{t}$ µg·h/mL
050/ I	Single Dose, Healthy Volunteers (HV)	Randomized, double-blind, single oral dose rising, fasted	TQ 4 to 600 mg or placebo	75M HV (18-35 y)	NR[a]	5.45[a]	2479[a]	361.4[a] (15.1 days)	6.05 - 273.0[a]	12.3[a]	NA[a]		0.739 - 97.69[a]
					Whole blood (600 mg dose) [a]: T_{max} = 10.7 hours, $t_{½}$ = 14 days (335.3 hours), $AUC_{(0-t)}$ = 164.6 µg h/mL, $AUC_{(0-inf)}$ = 193.4 µg h/mL								
052/ I	Single Dose, HV	Randomized, parallel-group, single oral dose, fasted	TQ 100 mg	18M HV (18-32 y)	0.309	5.32	2690 (34.8 L/kg)		46.7	12			
			TQ 200 mg						96.5				
			TQ 400 mg						183.8				
003/ I	Single Dose, HV	Randomized open label, parallel group, fasting/fed	TQ 400 mg	16M/16F HV (19-54 y)		NA							
022/ I	Single Dose, HV	Open label, parallel group, fasting/fed	TQ 200 mg, Fed	20M/20F HV (21-54 y)				372 (15.5 days)	166	14.0		0.070	
			TQ 200 mg, Fasting					369.6 (15.4 days)	122	13.0		0.051	

Study No./ Phase	Study Type	Study Design	Doses	Sample Size	ka (1/h)	CL/F (L/h)	V/F (L)	t½ (h)	Cmax (ng/mL)	Tmax (hrs)	Cmin	AUC$_{tau}$ µg·h/mL	AUC$_{t}$ µg·h/mL
TAF 114582/ I	Cardiac Safety Assessment	Randomized, single-blind, parallel group, multiple oral dose	TQ 400 mg OD for 3 days,	181 M/ 79 F HV (251 completed) (18-63 years)					724	12.0			41.90
			TQ 300 mg single dose						186	15.0			10.61
			TQ 600 mg single dose Placebo Moxifloxacin						422	12.0			22.99
014/ I	Relative Bio-availability, HV	Open label, randomized, relative bio-availability of 3 oral formulations	TQ 400 mg OD for 3 days (fed) (3 TQ formulations)	43M/15F HV (20-60 years)				409 (17 days)	758	61.7		315	310
								412 (17.2 days)	741	59.0		302	299
								443 (18.5 days)	795	60.7		330	326

Table 6 (continued): Summary of studies and design

Study No./ Phase	Study Type	Study Design	Doses	Sample Size	ka (1/h)	CL/F (L/h)	V/F (L)	t½ (h)	Cmax (ng/mL)	Tmax (hrs)	AUC_t µg·h/ mL
051/ I	Safety and tolerance	Randomized, placebo controlled	Capsule, 200 mg once weekly x 10 weeks, oral	30M/6F HV (23–46 years)				Week 10: 15.7 days	Day 1: 106 Week 10: 455	Day 1: 12.0 Week 10: 7.0	Day 1: 13.2 Week 10: 56.0 [b]
			Capsule 400 mg once weekly x 10 weeks, oral					Week 10: 20.0 days	Day 1: 249 Week 10: 783	Day 1: 12.0 Week 10: 12.0	Day 1: 27.8 Week 10: 82.1 [b]
			Capsule, 600 mg once weekly x 10 weeks, oral					Week 10: 28.8 days	Day 1: 252 Week 10: 707	Day 1: 9.0 Week 10: 7.0	Day 1: 30.9 Week 10: 78.3 [b]
054/ I	Malaria Challenge Study, HV	Randomized, double-blind, multiple oral dose (fed)	Multiple [c]	12M HV (19-36 years)				Median: 468 (19.5 days) Mean: 504 (21 days)	Median: 353: Mean: 358	Median: 11.9 Mean: 12.2	

Study No./ Phase	Study Type	Study Design	Doses	Sample Size	ka (1/h)	CL/F (L/h)	V/F (L)	t½ (h)	Cmax (ng/mL)	Tmax (hrs)	Cmin	AUC_∞ µg·h/ mL	AUC_t µg·h/ mL
015/ I	Drug-Drug Interaction Studies, HV	Open-label, Sngle sequence, desipramine interaction	Multiple [d]	20M/14 F HV (25-60 years)				436 (18.2 days)	496	Median: 24.0 Range: 0.0 – 84	Increased following each of the three daily TQ doses	275	
040/ I	Drug-Drug Interaction, HV	Open label, Two period, non-randomized, crossover, flurbiprofen, caffeine and midazolam interaction	TQ 200 mg bid for 3 days, midazolam 5 mg (Day 3), flurbiprofen 50 mg and caffeine 200 mg (Day 4)	18M/10 F HV (18-49 years)	No TQ PK data provided								

Table 6 (continued): Summary of studies and design

Study No./ Phase	Study Type	Study Design	Doses	Sample Size	ka (1/h)	CL/F (L/h)	V/F (L)	t½ (h)	Cmax (ng/mL)	Tmax (hrs)	Cmin	AUC_∞ µg·h/mL	AUC_t µg·h/mL
053/ I	Malaria Challenge Study, HV	Randomized, double-blind, single dose, placebo-control, fasted Malaria challenge study	TQ 600 mg po single dose (n = 4) or placebo (n = 2) 1 day pre-challenge	4 M/2 F HV, (19-30 years)					Blood: 417 – 489				
					Blood C_{max} (participant who developed parasitemia): 244 ng/mL. Plasma C_{max} (parasitemia) 182 ng/mL: compared to 3 participants with no parasitemia 238 – 302 ng/mL								
044 / II	Malaria Prop-hylaxis Study non-immune Thai soldiers	Double-blind, Randomized, placebo-controlled	TQ 400 mg x 3d, then 400 mg monthly	104M (TQ) and 101M (placebo) (21-48 years)	0.694	3.20	1820			8.62			

Study No./ Phase	Study Type	Study Design	Doses	Sample Size	ka (1/h)	CL/F (L/h)	V/F (L)	t½ (h)	Cmax (ng/mL)	Tmax (hrs)	Cmin	AUC_∞ µg·h/mL	AUC_t µg·h/mL
049/ II	Malaria Pro-phylaxis in non-immune Australian army troops	Open label, randomized, parallel group	PQ 7.5 mg OD for 14 days	Cohort AMI 001: 210 Cohort AMI 002: 131 Cohort AMI 003: 158 Total: 499	Data unavailable								
			TQ 200 mg OD for 3 days	Cohort AMI 003: 406 Total: 406									
			TQ 200 mg bd for 3 days	Cohort AMI 001: 86 Cohort AMI 002: 75 Total: 161									
			TQ 400 mg OD for 3 days	Cohort AMI 001: 288 Cohort AMI 002: 158 Total: 446									

Table 6 (continued): Summary of studies and design

Study No./ Phase	Study Type	Study Design	Doses	Sample Size	ka (1/h)	CL/F (L/h)	V/F (L)	t½ (h)	Cmax (ng/mL)	Tmax (hrs)	Cmin	AUC∞ µg·h/mL	AUCt µg·h/mL
047/ II	Malaria Pro-phylaxis Study, HV and patients	Open label, randomized, dose ranging	CQ followed by: TQ 300 mg OD for 7 days, TQ 500 mg OD for 3 days (x2), TQ 500 mg single dose or no treatment	55M/41 F HV (16-53 y)	0.414	2.77	V2/F: HV: 1603.6 PT: 1053.6	406 (16.9 days)	292	8.0		136	109
					Whole blood: CL/F = 1.77 L/h, V2/F = 851.9 L, 0.33 1/h								

Study No./ Phase	Study Type	Study Design	Doses	Sample Size	ka (1/h)	CL/F (L/h)	V/F (L)	t½ (h)	Cmax (ng/mL)	Tmax (hrs)	Cmin	AUC∞ µg·h/mL	AUCt µg·h/mL
058/ II	*P vivax* Treatment Study	Randomized, active-control, double-blind, double-dummy	TQ 400 mg OD for 3 days or 1000 mg CQ 2days, 500 mgCQ 1 day, 15 mg PQ 14 days	57M/13F (20-55 years)	0.132	3.37	V2/F: 759			T_{lag}: 1.35 (4.4)			
			TQ 600 mg OD for 1 day or CQ +PQ eradication as above		PK data combined with that from Study 14								
006/ II	Malaria Pro-phylaxis Study in Endemic Malarial Area, Gabon	Randomized, double-blind, placebo-controlled	TQ 25 mg OD for 3 days	80 (ITT for this dose)									
			TQ 50 mg OD for 3 days	86 (ITT for this dose)									
			TQ 100 mg OD for 3 days	82 (ITT for this dose)									
			TQ 200 mg OD for 3 days	84 (ITT for this dose)									

Study No./ Phase	Study Type	Study Design	Doses	Sample Size	ka (1/h)	CL/F (L/h)	V/F (L)	t½ (h)	Cmax (ng/mL)	Tmax (hrs)	Cmin	AUC∞ µg·h/mL	AUCt µg·h/mL
TAF112 582/ II	*P vivax* Treatment Study	Randomized, double-blind, parallel group, active-controlled	CQ followed by TQ 50, 100, 300 or 600 mg single dose, or CQ followed by PQ or no treatment	329 (TQ-treated) (16-74 y)	0.154	3.21 (M) 2.80 (F)	V2/F: 791						
TQ-2016-02	Malaria Pro-phylaxis	Randomized, double-blind	200 mg TQ Days 1, 2, 3, 10 Placebo	12 TQ							172 ng/mL Day 2		
030/ III	Malaria Pro-phylaxis	Randomized, double-blind											
033/ III	Malaria Pro-phylaxis Study non-immune Australian army troops	Double-blind, randomized, mefloquine positive control	TQ 200 mg x 3d, then 200 mg weekly or MQ 250 mg x 3 d, then 250 mg weekly	632 M/ 22 F HV (18-51 y)	0.243	4.53 (0.056 L/h/kg)	1917 (23.7 L/kg)	304.8 (12.7 days)					

2.2. Paediatric data

There were 229 adolescent subjects (ages 12 to 17 years) and 1 paediatric subject (age 4 years) received various doses of tafenoquine in 6 studies (Studies 006, 030, 036, 043, 045, and 047). The majority of these subjects (n=216) were enrolled in Study 006, with only 1 or 2 subjects included in each of the remaining 5 studies. Only one subject (a girl in Study 036) was under the age of 12 years; the remaining 223 subjects were 12 to 17 years of age.

This application is not for use in children, only in adults.[1]

2.3. Good clinical practice

Most studies state that they have complied with *Guidance on Good Clinical Practice* in the study report. For Studies 051, 052, 053, 054 there is no statement but these studies were conducted in the 1990's which may be the explanation. The other studies have a statement of being conducted in accordance with good clinical practice.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic information

The safety and PK of single tafenoquine doses in healthy individuals were assessed in Studies 050, 052, 003 and 022. Studies 050 and 052 assessed the safety and tolerability of single dose tafenoquine and the kinetics of the study drug as secondary and primary objectives respectively. Effect of food on the PK of single dose tafenoquine was assessed in Study 022. Different loading doses in healthy individuals were evaluated in Studies TAF114582 and 014; different weekly regimens in healthy individuals were evaluated in Study 051. In each, the safety, tolerability and PK of the drug were assessed. Pharmacological parameters were examined in a number of studies that were performed to determine efficacy of tafenoquine. PK data from prophylactic, treatment and challenge studies were assessed in Studies 053, 054, 006, 030, 033, 044, 049, 047, 043, and 058. Because prophylaxis is indicated for healthy individuals, all of these studies except Study 058 were performed in healthy populations. Study 058 was conducted in participants with confirmed symptomatic Pv. PK-PD data were reported in Study TAF112582. In 3 other studies (Studies 001, 036 and 043) PK data could not be obtained for procedural reasons, even though it was intended.

Table 7: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK Single dose	050	*
		052	*
		022	*
	Multi dose	051	*

[1] Sponsor comment: This application is not for use in children, only in adults, as the sponsor believes additional paediatric data are required to confirm the safety and tolerability of the approved adult dose in children. Further paediatric studies are planned under an FDA approved paediatric study plan

PK topic	Subtopic	Study ID	*
		TAF114582 014 033 TAF112582 (201393) TQ-2016-2 044	* * * * * * *
	Bioequivalence † - Single dose	TQ-2016-01	*
	- Multi dose	014	*
	Food effect	022 003	*
	Other special population	TAF114582	*
Genetic/gender related PK	Males versus females	014 003	* *
PK interactions	Desipramine	015	*
	Midazolam, flurbiprofen, caffeine	040	*
	Chloroquine	TAF106491	*
Population PK analyses	Healthy subjects	044-033	*

* Indicates the primary PK aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication. **see table below.

Table 8: Pharmacokinetic results excluded from consideration

Study ID	Subtopics	PK results excluded
Study 003	Effect of food and gender	No results

3.2. Summary of pharmacokinetics

3.2.1. Physicochemical characteristics of the active substance

A granule-filled capsule was developed for clinical studies and used in all studies up to those that were started after 2016, with one exception. The granule was also incorporated into a direct compression tablet formulation with additional excipients and film-coated for used in Study 014 (a bioequivalence study comparing the capsule and tablet formulations).

The marketing formulation is tafenoquine immediate release tablets for oral administration containing active ingredient (125 mg of tafenoquine succinate, which is equivalent to 100 mg of the free base). Study TQ-2016-01 has shown that the PK (AUC, C_{max}, $t_{½}$) following administration of 200 mg (2 x100 mg) of the marketing formulation are equivalent to historic values (Study 022) of the PK of 200 mg of the capsule formulation used in prior clinical work.

3.2.2. Pharmacokinetics in healthy subjects

3.2.2.1. Absorption

Dissolution studies of tafenoquine in simulated gastric fluid demonstrated complete dissolution within 30 minutes. These results inform on the long apparent absorption phase of the drug, which may be due to a distal gastrointestinal absorption site combined with the drug's slow clearance since T_{max} is a function of both absorption and elimination rates.

The consolidated data from studies clinical PK data from Studies 001, 002, 003, 004, 005, 014, 015, 033, 044 and 058 (866 participants in total) were used to determine population pharmacokinetics using a one-compartment model. These determined the following parameters:

- T_{max}: 7 hours
- $T_{1/2}$: 17 days
- $C_{max,ss}$: 300 ng/mL
- CL/F: 4.17 L/hour
- Vd/F: 2470 L
- AUC $_{(0\text{-}1\ week)}$: Day 1, 13.2 ± 1.9 (ng·h/mL); Study 51 showed accumulation with repeated dosing and AUC at Week 10 was 56.0 ± 18.4 (ng·h/mL).

In Study 051, healthy volunteers received 10 weekly administrations of one of 200 mg or 400 mg while fasting. PK parameter values are given in Table 9. The accumulation ratio for the 200 mg dose was approximately 4.

Table 9: Summary of plasma tafenoquine PK parameters (Study 051)

Dose mg	$AUC_{(0\text{-}1\ week)}$ ng·h/mL		C_{max} ng/mL		T_{max} h		$t_{½}$ Days
	Day 1	Week 10	Day 1	Week 10	Day 1	Week 10	Week 10
200	13.2 ± 1.9	56.0 ± 18.4	106 ± 20	455 ± 456	12.0 (8.0–24.0)	7.0 (0.0–24.0)	15.7 ± 2.0
400	27.8 ± 4.9	82.1 ± 14.2	249 ± 74	783 ± 196	12.0 (4.0–24.0)	12.0 (6.0–24.0)	20.0 ± 3.5

3.2.2.2. Bioavailability

Following administration of a single dose of tafenoquine to healthy males in Study 050 showed AUC and C_{max} to be dose proportional (Figures 1 and 2).

Figure 1: Dose–C_{max} proportionality of tafenoquine (Study 050)

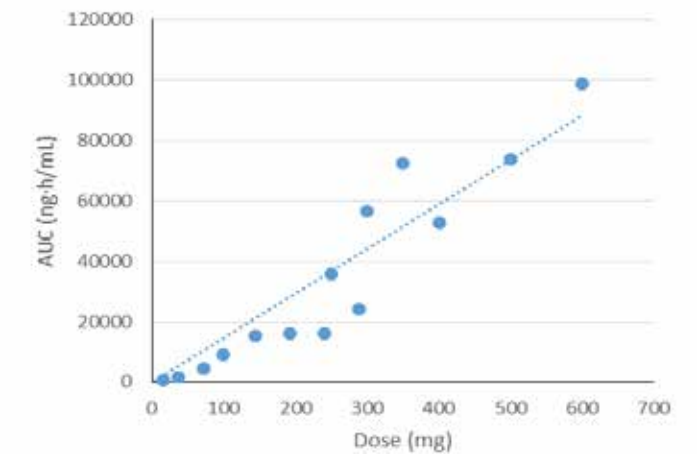
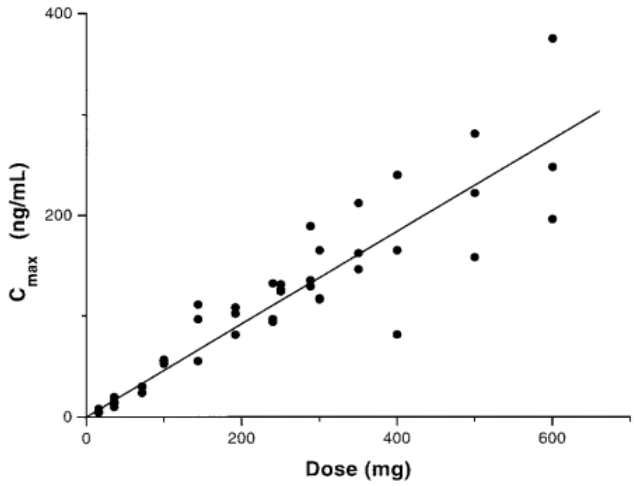


Figure 2: Dose–$AUC_{(0\text{-}tlast)}$ proportionality of tafenoquine (Study 050)



Food effect

Tafenoquine plasma concentrations were higher after administration of a single dose of tafenoquine in fed compared with fasting conditions, with mean fed: fasted ratios of 1.41 (AUC) and 1.31 (C_{max}). Tmax and $t_{½}$ were similar under fasting and fed states, with mean AUC (Fed: 69.7 ± 24.4 ng·h/mL; Fasted: 51.1 ± 22.0) and C_{max} (Fed: 166 ± 84 ng/mL; Fasted: 122 ± 43). T_{max} (13.0 and 14.0 hours) and $t_{½}$ (15.4 and 15.5 days) were similar under fasting and fed states. Variability between individuals (coefficient of variation) in $AUC_{(0\text{-}inf)}$ and C_{max} was 38.8% and 40.8%, respectively with no increase in variability associated with food intake.

Population PK analyses demonstrated after the recommended regimen of 200 mg/day times three days for loading followed by 200 mg weekly, trough tafenoquine values even in the non-fed state were above the value of 80 ng/mL by the end of the loading dose. By the sixth weekly dose, exposure in the fasted state is predicted to equal exposure in the fed state.

Effect of gender and smoking

The effect of gender and smoking status, on PK was evaluated in Study 014. Females had greater exposure than males; non-smokers had somewhat greater exposure than smokers (Table 10). The differences in PK parameters between genders can be explained by differences in weight, thus showing that exposure is essentially identical on an mg drug per kg body weight basis.

Table 10: Results of Study 014; effect of gender and smoking status on $AUC_{0\text{-}inf}$ and C_{max} (least square means)

Numbers in parenthesis	$AUC_{0\text{-}inf}$ (µg·h/mL)*	C_{max} (ng/mL)
Females (15)	351	862
Males (43)	288	680
Non-Smokers (27M:9F)	336	830
Smokers (16M: 6F)	300	706

*Abbreviations: $AUC_{0\text{-}inf}$: area under the curve from zero to infinity. C_{max}: Maximum concentration. F: female. M: male.

3.2.2.3. Distribution

In Study 052, healthy male volunteers were administered one dose of 100 mg, 200 mg and 400 mg while fasting. Blood and calculated RBC concentrations were 2.0 and 3.4 times higher than corresponding plasma concentrations and there was no change in RBC accumulation over time. In humans, >99.5% of tafenoquine is bound to plasma protein.

3.2.2.4. Metabolism

Human urine (pre dose and 48 to 72 hours following first dose) and plasma (pre dose, 60 and 84 hours following first dose) were obtained from Study 014 following oral tafenoquine 400 mg once daily for 3 days. Small amounts of more than 18 drug related components were detected in human urine by HPLC-MS, thought to result from multiple sites of metabolism (or degradation) via O-demethylation, O-dearylation, N-dealkylation, deamination, oxidation, N-carbamylation, N-acetylation and glucuronide conjugation. None of these were identified in plasma. When tafenoquine was administered to humans at 400 mg per day x 3 days, only parent tafenoquine was extractable in plasma drawn 80 hrs after the first dose. There is no further characterisation of in vivo metabolism of this drug in this submission.

3.2.2.5. Excretion

Human radiolabelled mass balance studies have not been conducted to characterise the clinical excretion of tafenoquine. In animals, excretion of radioactivity (from labelled tafenoquine) was slow. Animal data suggested extensive reabsorption of biliary excreted radioactivity and enterohepatic circulation of drug and/or metabolites.

3.2.2.6. Intra and inter individual variability of pharmacokinetics

This was found to be approximately 24% for CL and V_d from the population PK analysis, summarised in Table 11.

Table 11: Population PK parameters (Studies 001, 002, 003, 004, 005, 014, 15, 033, 044 and 058)

Parameters (Units)	Final Estimate	Bootstrap 95% CI		Inter-individual Variability*
		Lower	Upper	
$CL/F\ (L/h) = \theta_{CL} \times (WT/75)^{\theta_{CL\text{-}WT}} \times (AGE/25)^{\theta_{CL\text{-}AGE}}$				23.6%
θ_{CL}	4.17	4.080	4.230	
θCL-WT	0.552	0.474	0.637	
θCL-AGE	-0.200	-0.267	-0.138	
$V/F\ (L) = \theta_{V} \times (WT/75)^{\theta_{V\text{-}WT}} \times (\theta_{V\text{-}FOOD})^{FOOD}$				24.1%
θ_{V}	2470	2340	2630	
θV-WT	0.781	0.652	0.901	
θV-FOOD	0.822	0.761	0.861	
k_a (1/h)	0.359	0.321	0.384	54.1%
ω^2_{CL}	0.0555	0.0462	0.0618	
$COV_{CL,V}$	0.0289	0.0186	0.0315	
ω^2_{V}	0.0583	0.0444	0.0606	
$\omega^2_{k_a}$	0.293	0.203	0.378	
σ^2	0.0488	0.0436	0.0553	

*The magnitude of inter-individual variability was presented as the coefficient of variation.CI, confidence interval; COV, covariance; ω^2: variance of the inter-individual random effect; δ^2: variance of the proportional residual random effect. CL = clearance, V=volume, K_a = first order absorption rate. NOTE: Final estimate and inter-individual variability were from NONMEM estimates. FOOD = 0 for fasted and 1 for fed.

3.2.3. Pharmacokinetics in the target population

The target for this drug will essentially be healthy people (as malaria prophylaxis). Population PK analysis predicts that the recommended prevention regimen will achieve trough levels >80 ng/mL in >95% of subjects.

3.2.4. Pharmacokinetics in special populations

3.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

Not applicable.

3.2.4.2. Pharmacokinetics in subjects with impaired renal function

Not applicable.

3.2.4.3. Pharmacokinetics according to age

There is a small amount of data for adolescents (contained in Section *Postmarketing experience* below)

3.2.4.4. Pharmacokinetics related to genetic factors

Not applicable.

3.2.4.5. Pharmacokinetics in other special population / with other population characteristic

The effect of gender and smoking status, on PK was evaluated in Study 014. Females had greater exposure than males; non-smokers had somewhat greater exposure than smokers. The differences in PK parameters between genders were explained by differences in weight, as the mean female body weight in Study 014 was 63.6 kg compared to a mean male body weight of 77.0 kg. AUC/1M/K for females was 352 units/6.25 mg per kg =56 and AUC for males was 288 units/5.2 mg/kg = 55, showing that exposure is essentially similar on an mg drug per kg body weight basis for the two genders. Results are shown in Tables 12 to 16.

Table 12: Population PK parameters (Studies 001, 002, 003, 004, 005, 014, 15, 033, 044 and 058)

Parameters (Units)	Final Estimate	Bootstrap 95% CI		Inter-individual Variability*
		Lower	Upper	
$CL/F\ (L/h) = \theta_{CL} \times (WT/75)^{\theta_{CL\text{-}WT}} \times (AGE/25)^{\theta_{CL\text{-}AGE}}$				23.6%
θ_{CL}	4.17	4.080	4.230	
θCL-WT	0.552	0.474	0.637	
θCL-AGE	-0.200	-0.267	-0.138	
$V/F\ (L) = \theta_{V} \times (WT/75)^{\theta_{V\text{-}WT}} \times (\theta_{V\text{-}FOOD})^{FOOD}$				24.1%
θ_{V}	2470	2340	2630	
θV-WT	0.781	0.652	0.901	
θV-FOOD	0.822	0.761	0.861	
k_a (1/h)	0.359	0.321	0.384	54.1%
w^2_{CL}	0.0555	0.0462	0.0618	
$COV_{CL,V}$	0.0289	0.0186	0.0315	
w^2_{V}	0.0583	0.0444	0.0606	
$w^2_{k_a}$	0.293	0.203	0.378	
s^2	0.0488	0.0436	0.0553	

*The magnitude of inter-individual variability was presented as the coefficient of variation.CI, confidence interval; COV, covariance; w^2: variance of the inter-individual random effect; δ^2: variance of the proportional residual random effect. CL = clearance, V=volume, K_a = first order absorption rate. NOTE: Final estimate and inter-individual variability were from NONMEM estimates. FOOD = 0 for fasted and 1 for fed.

Table 13: Summary of statistical analysis of $AUC_{(0-inf)}$ comparing CYP substrates administered alone and with/after tafenoquine

Drug	CYP	Comparison	Ratio	90% CI*	CV% (within)
Desipramine	CYP2D6	C:A	0.94	(0.89, 1.00)**	11.7
Midazolam	CYP3A4	B2: A1	0.88	(0.83, 0.94)	12.1
Flurbiprofen	CYP2C9	B3 : A2	1.13	(1.09, 1.16)	6.7
Caffeine	CYP1A2	B3 : A2	1.01	(0.98, 1.05)	7.4

*Adjusted 90% confidence interval (to account for the interim analysis). **Confidence interval 0.999 is rounded to 1.00. A, Desipramine alone; A1, Midazolam 5 mg; A2, Flurbiprofen 50 mg + caffeine 200 mg; B2, Midozolam 5 mg + tafenoquine 400 mg; B3, Flurbiprofen 50 mg + Caffeine 200 mg (post administration of tafenoquine 400 mg); C, Desipramine + tafenoquine. CI: confidence interval; CV: coefficient of variation; ND: not determined.

Table 14: Summary of statistical analysis of C_{max}, comparing CYP substrates administered alone and with/after tafenoquine

Drug[(i)]	CYP	Comparison	Ratio	90% CI	CV% (within)
Desipramine	CYP2D6	C:A	1.04	(0.98, 1.10)	11.1
Midazolam	CYP3A4	B2: A1	0.97	(0.83, 1.13)	32.0
Flurbiprofen	CYP2C9	B3 : A2	0.98	(0.91, 1.04)	13.9
Caffeine	CYP1A2	B3 : A2	0.95	(0.89, 1.01)	13.6

A, Desipramine alone; A1, Midazolam 5 mg; A2, Flurbiprofen 50 mg + caffeine 200 mg; B2, Midozolam 5 mg + tafenoquine 400 mg; B3, Flurbiprofen 50 mg + Caffeine 200 mg (post administration of tafenoquine 400 mg); C, Desipramine + tafenoquine.

Table 15: Summary of statistical analysis of $AUC_{(0-inf)}$ comparing CYP substrates administered alone and with/after tafenoquine

Drug	CYP	Comparison	Ratio	90% CI*	CV% (within)
Desipramine	CYP2D6	C:A	0.94	(0.89, 1.00)**	11.7
Midazolam	CYP3A4	B2: A1	0.88	(0.83, 0.94)	12.1
Flurbiprofen	CYP2C9	B3 : A2	1.13	(1.09, 1.16)	6.7

Drug	CYP	Comparison	Ratio	90% CI*	CV% (within)
Caffeine	CYP1A2	B3 : A2	1.01	(0.98, 1.05)	7.4

*Adjusted 90% confidence interval (to account for the interim analysis). **Confidence interval 0.999 is rounded to 1.00. A, Desipramine alone; A1, Midazolam 5 mg; A2, Flurbiprofen 50 mg + caffeine 200 mg; B2, Midozolam 5 mg + tafenoquine 400 mg; B3, Flurbiprofen 50 mg + Caffeine 200 mg (post administration of tafenoquine 400 mg); C, Desipramine + tafenoquine. CI: confidence interval; CV: coefficient of variation; ND: not determined.

Table 16: Summary of statistical analysis of C_{max}, comparing CYP substrates administered alone and with/after tafenoquine

Drug*	CYP	Comparison	Ratio	90% CI	CV% (within)
Desipramine	CYP2D6	C:A	1.04	(0.98, 1.10)	11.1
Midazolam	CYP3A4	B2: A1	0.97	(0.83, 1.13)	32.0
Flurbiprofen	CYP2C9	B3 : A2	0.98	(0.91, 1.04)	13.9
Caffeine	CYP1A2	B3 : A2	0.95	(0.89, 1.01)	13.6

*A, Desipramine alone; A1, Midazolam 5 mg; A2, Flurbiprofen 50 mg + caffeine 200 mg; B2, Midozolam 5 mg + tafenoquine 400 mg; B3, Flurbiprofen 50 mg + Caffeine 200 mg (post administration of tafenoquine 400 mg); C, Desipramine + tafenoquine.

3.2.5. Population pharmacokinetics

3.2.5.1. PopPK analysis

A population PK analysis was conducted consolidating clinical PK data from Studies 001, 002, 003, 004, 005, 014, 015, 033, 044 and 058. Covariates common to all 10 studies were age, weight, race, gender and meal schedule. The study comprised 866 participants across the studies. The total study population was 93.3% male; median age 25 years, mean weight 75.0 kg and 72.3% Caucasian/White. The majority of participants (89.4%) took tafenoquine under fed conditions. Key parameters from this analysis are summarised above. A one-compartment PK model with first-order absorption and elimination processes was parameterised in terms of apparent CL/F, V/F and ka. Co-variate (gender, age, race, body weight and meal) analysis was performed on the base PK model. Gender and race were confounded with weight and were not explored further.

Median tafenoquine steady-state (ss) trough plasma concentrations after simulation of the reference regimen decreased as weight increased but were predicted to remain higher than the required threshold of 80 ng/mL in the majority of individuals at all levels of body weight and the vast majority of individuals even up to 100 kg.

3.2.6. Pharmacokinetic interactions

Studies 015 and 040 were Phase I clinical trial conducted to evaluate the effect of tafenoquine on the metabolism of multiple cytochrome P450 (CYP) substrates in healthy volunteers. Comparison of each of desipramine, midazolam, flurbiprofen and caffeine PK parameters after administration as a single agent or after tafenoquine demonstrate that each of $AUC_{(0\text{-inf})}$, C_{max}, and $t_{½}$ were similar Tables 17A-C). Tafenoquine does not significantly inhibit or induce CYP2D6, CYP3A4, CYP2C9 or CYP1A2, since in Phase I studies, the PK parameters of the CYP2D6

substrate desipramine, the CYP3A4 substrate midazolam, the CYP2C9 substrate Flurbiprofen and the CYP1A2 substrate caffeine were unaffected by co-administration of tafenoquine.

Tafenoquine was a potent inhibitor of renal multidrug and toxin extrusion transporters (MATE) and organic cation transporter 2 in vitro. Since inhibition of these transporters may lead to increased exposure to medications that they excrete, when tafenoquine is co-administered with dofetilide and procainamide, the safety and/or efficacy of the latter drugs may need to be evaluated (no data on these interactions in clinical studies to date).[2]

Table 17A: Summary of statistical analysis of $t_{½}$; comparing CYP substrates administered alone and with/after tafenoquine

Drug	CYP	Comparison#	Ratio	90% CI	CV% (within)
Desipramine	CYP2D6	C-A	-2.61	(-6.07, 0.86)	ND
Midazolam	CYP3A4	B2:A1	0.98	(0.89, 1.08)	18.8
Flurbiprofen	CYP2C9	B3:A2	1.15	(1.10, 1.21)	9.1
Caffeine	CYP1A2	B3:A2	1.03	(0.99, 1.08)	8.8

All comparisons listed are a ratio of regimen 1 to regimen 2, except desipramine, which displays the difference between $t_{½}$ of regimens 1 and 2 (i.e. $t_{½}$ decreased by 2.61 hours on average, in the presence of tafenoquine). A, Desipramine alone; A1, Midazolam 5 mg; A2, Flurbiprofen 50 mg + caffeine 200 mg; B2, Midazolam 5 mg + tafenoquine 400 mg; B3, Flurbiprofen 50 mg + Caffeine 200 mg (post administration of tafenoquine 400 mg); C, Desipramine + tafenoquine. CI, confidence interval; CV, coefficient of variation; ND= not determined.

Table 17B: Summary of statistical analysis of C_{max}, comparing CYP substrates administered alone and with/after tafenoquine

Drug*	CYP	Comparison	Ratio	90% CI	CV% (within)
Desipramine	CYP2D6	C:A	1.04	(0.98, 1.10)	11.1
Midazolam	CYP3A4	B2: A1	0.97	(0.83, 1.13)	32.0
Flurbiprofen	CYP2C9	B3 : A2	0.98	(0.91, 1.04)	13.9
Caffeine	CYP1A2	B3 : A2	0.95	(0.89, 1.01)	13.6

*A, Desipramine alone; A1, Midazolam 5 mg; A2, Flurbiprofen 50 mg + caffeine 200 mg; B2, Midozolam 5 mg + tafenoquine 400 mg; B3, Flurbiprofen 50 mg + Caffeine 200 mg (post administration of tafenoquine 400 mg); C, Desipramine + tafenoquine.

[2] Sponsor comment: The sponsor has conservatively included this theoretical risk statement in the approved PI (Attachment 1).

Table 17C: Summary of statistical analysis of $t_{½}$ comparing CYP substrates administered alone and with/after tafenoquine

Drug	CYP	Comparison[#]	Ratio	90% CI	CV% (within)
Desipramine	CYP2D6	C-A	-2.61	(-6.07, 0.86)	ND
Midazolam	CYP3A4	B2:A1	0.98	(0.89, 1.08)	18.8
Flurbiprofen	CYP2C9	B3:A2	1.15	(1.10, 1.21)	9.1
Caffeine	CYP1A2	B3:A2	1.03	(0.99, 1.08)	8.8

[#] All comparisons listed are a ratio of regimen 1 to regimen 2, except desipramine, which displays the difference between $t_{½}$ of regimens 1 and 2 (i.e. $t_{½}$ decreased by 2.61 hours on average, in the presence of tafenoquine). A, Desipramine alone; A1, Midazolam 5 mg; A2, Flurbiprofen 50 mg + caffeine 200 mg; B2, Midazolam 5 mg + tafenoquine 400 mg; B3, Flurbiprofen 50 mg + Caffeine 200 mg (post administration of tafenoquine 400 mg); C, Desipramine + tafenoquine. CI: confidence interval; CV: coefficient of variation; ND: not determined.

3.3. Evaluator's overall conclusions on pharmacokinetics

The PK data for tafenoquine was adequate, although specific excretion studies were not performed in humans.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic information

As mentioned above, many of the dose ranging, PK studies were also clinical efficacy studies.

Table 18: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on Prophylaxis against Pf	053	*§
		054	*§
		030	*§
		006	*§‡
		043	*§
	Parasite challenge	TQ-2016-02	*§
	Effect on ECG (QTc prolongation)	Study TAF114582	*§

PD Topic	Subtopic	Study ID	*
	malaria treatment	Study 047	*

*Indicates the primary PD aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable. # Study 058 contributed a small amount of PK data to the population PK modelling. This is data is not documented in the study report.

4.2. Summary of pharmacodynamics

4.2.1. Mechanism of action

Tafenoquine kills the developing asexual, developing exoerythrocytic, and latent hypnozoites of malaria parasites. The mechanism of action is unknown, but is hypothesised to involve redox reactions.

4.2.2. Pharmacodynamic effects

4.2.2.1. Primary pharmacodynamic effects

The primary PD effect is prevention of the development of malaria in persons exposed. In relation to this submission, this will generally be for non-immune persons travelling to areas of endemnicity. For best effect, the drug needs to work on both the erythrocytic phases and also exo-erythrocytic (liver) phases, to prevent disease developing weeks or months after leaving the endemic area. Post-exposure prophylaxis to kill dormant forms and prevent relapse requires an 8-aminoquinoline, the only category of antimalarial agents known to have clinical anti-hypnozoite activity (tafenoquine and primaquine). For this purpose, primaquine dosing (30 mg per day for an adult) is extended to 14 days after leaving the endemic region. The initial malaria challenge Studies 053 and 054 showed that the drug tafenoquine had protective efficacy. The field studies confirmed this. Subsequent studies went on to look at loading and ongoing weekly dosing efficacy.

4.2.3. Time course of pharmacodynamic effects

4.2.3.1. *Studies 006 and 043*

The first investigation was whether a 3 day loading dose alone would provide sufficient prophylactic efficacy. In Study 006, a loading dose of 25 to 200 mg per day for 3 days alone provided 100% prophylactic efficacy (PE) in semi-immunes for 7 weeks. But Study 043 showed that in the group treated with a loading dose only of 400 mg/day for 3 days, without ongoing therapy, efficacy dropped to 72% efficacy in semi-immune subjects by assessment at 15 weeks (Table 19), indicating that for adequate protection, the loading dose needed to be followed by regular dosing (as shown in other groups in Study 043).

Table 19: Protective efficacy at End of Study 043 (Efficacy population)

	Placebo N = 59	Load-Only Tafenoquine 400 mg N = 54
Positive for Parasitemia	54 (92%)	14 (26%)
PE (%)		71.7
95% CI		(57.0%, 82.5%)

4.2.4. Relationship between drug concentration and pharmacodynamic effects

In Study 053, one volunteer in the tafenoquine developed Pf malaria after a single dose of tafenoquine 600 mg (and then sporozoite inoculation). Three did not. This subject had a lower peak blood and plasma concentration of the drug (244 ng/mL and 182 ng/mL) than the other subjects. Blood and plasma concentrations at the time of prophylactic failure were approximately 50 and approximately 60 ng/mL, respectively.

The results of the follow up Study 054, were slightly contradictory in that, 6 of 10 drug treated individuals developed asymptomatic parasitemia. It is impossible to know whether these individuals were mainly in the group that only received only 2 doses of tafenoquine (then post-exposure placebo). But even if this is the case, at least one subject who went on to have full course of tafenoquine developed parasitemia. This study was done prior to 2000. There was also slight disagreement between the initial and subsequent blinded reviewer of the blood films (in relation to one smear). The justification in the discussion is that the strain used is quite resistant to tafenoquine, but the same strain was used in Study 053.

In Study 044, in which participants were administered tafenoquine 400 mg monthly following tafenoquine 400 mg loading doses (daily for 3 days), 3 symptomatic breakthroughs occurred 6 to 12 weeks following prophylaxis. Of these 6 subjects, 2 subjects had Pv relapse with tafenoquine plasma concentrations between 20 and 21 ng/mL, and 1 subject had Pf relapse with tafenoquine concentration 38 ng/ml. Furthermore, 1 subject had Pv relapse during the prophylaxis phase with tafenoquine concentration of 40 ng/mL (the subject was found to have been non-compliant with medication). This level was one-third of the mean trough level of Thai soldiers who were compliant with medication and did not contract malaria during the same period of the study.

In Study TQ-2016-2 mean trough plasma levels in the treatment groups were 172.02 ng/mL (SD 31.58) at Day 2 after the first loading dose, and levels increased with each subsequent loading dose. Following administration of the final, post-loading dose on Day 10, tafenoquine plasma levels attained steady-state trough levels with a mean concentration of 378.14 ng/mL (SD 60.63) on Day 13 at the time of parasite inoculation. After this, slow decline in trough plasma levels occurred, but these remained higher than the required threshold of 80 ng/mL until the last sampling time point, where a mean circulating concentration of 174.12 ng/mL (SD 53.50) was determined. All these levels were well above the desired threshold of plasma concentration threshold (80 ng/mL).

Study 033 contributed a small amount of data to PD. In four subjects there was no relationship between individual PK estimates and relapse with Pv malaria in the follow up phase all of whom had similar drug concentrations to subjects who did not relapse.

It appears to be mainly on the basis of the results of Study 053 which showed that symptomatic breakthrough of malaria occurred when tafenoquine plasma concentrations were around 50 ng/mL. A plasma concentration of 80 ng/mL was then selected as the minimum target trough value for prevention of symptomatic malaria development in nonimmune individuals. The evaluator was unsure why this concentration was specifically chosen (except that it was greater than 50 ng/mL).[3]

4.2.5. Genetic, gender and age related differences in pharmacodynamic response

Not applicable.

[3]Sponsor comment: The break through dose is 40 ng/mL. The dose was titrated to achieve double the concentration to account for the risk of heavier, ADF males having a sub-protective concentration.

4.2.6. Pharmacodynamic interactions

Not applicable.

4.3. Evaluator's overall conclusions on pharmacodynamics

It appears to be on the basis of Study 054 that the target trough plasma concentration of tafenoquine of 80 ng/mL was chosen.[4]

It was difficult to assess which groups the patients who developed parasitemia were in (that is, the group fully treated, or the group just loaded) in Study 054. This is however, a very old study (on 12 individuals) and many larger studies have been done subsequently.

Data on PD and efficacy from Study 030 is unreliable because of problems with reliability of smears read locally in Kenya where the study was conducted. When these slides were re-read at a reference centre, there was a positive concordance value of only 12.4%.

Study TQ-2016-2, is a very small but well conducted study of a malaria challenge in which tafenoquine was 100% effective in prevented Pf. The mean plasma concentration in this study however was well above the proposed threshold. It would be useful to have a study of this nature for Pv to examine efficacy against relapse from the exo-erythrocytic phases.

Study 043 was the first major well-designed field study which showed 'proof of concept' of the current recommended dosing regimen, with good evidence of prophylactic efficacy. PK data was also planned from this study but the samples taken for this were unable to be processed, so there is no PK data. A threshold dose of 200 mg daily x 3 days followed by 200 mg weekly was shown in Study 043 to provide a dosage regimen at which adequate malaria prophylaxis was seen.

5. Dosage selection for the pivotal studies

5.1. Pharmacokinetics and pharmacodynamics: dose finding studies

Phase I studies that determined if tafenoquine had prophylactic activity against Pf malaria and examined the utility of tafenoquine against challenge with Pf asexual blood stage parasites in non-immune participants; characterise the exposure-response relationship for tafenoquine were Studies 053, 054 and TQ-2016-02.

For the indication 'prophylaxis of malaria' while in the endemic region, subjects were randomly assigned to one or more tafenoquine groups, and to a placebo control and/or mefloquine positive control group. In some early studies (Studies 006, 043, 058) only a 3 day loading dose was administered. In most studies, the loading dose was followed by weekly (or monthly in Study 044) drug administration. The individual dose used on each day of treatment varied between 25 mg to 400 mg. Studies 030, 033, 043 and 045 evaluated the 200 mg based anticipated clinical regimen: a loading dose of 200 mg per day x 3 days followed by administration of 200 mg weekly.

[4] Sponsor comment: Breakthrough concentrations at which malaria occurred in the Royal Thai Army study (Study 044) and the two prior sporozoite challenge studies (Study 053 and Study 054) to support 80 ng/mL as the $C_{min, SS}$ for protection in heavier males (> 100 kg). The dose was titrated to achieve double the concentration to account for the risk of heavier, ADF males having a sub-protective concentration. This was established in the population PK analysis of 10 clinical studies.

Studies in non-immune persons, the main population for which prophylaxis is intended, showed that symptomatic breakthrough of malaria occurred when tafenoquine plasma concentrations were < 50 ng/mL (Study 053). This was also confirmed by logistic regression in Study TAF112582. Consequently, a plasma concentration of 80 ng/mL was selected as the minimum target trough value for prevention of symptomatic malaria development in non-immune individuals. Population PK analysis predicted that the recommended prevention regimen will achieve trough levels >80 ng/mL in >95% of subjects.

5.2. Phase II dose finding studies

This included the following studies, discussed above and in the section *Clinical efficacy* for Studies 044, 006, 049, 047, and TAF112582.

5.3. Phase III pivotal studies investigating more than one dose regimen

Study 045 (Phase II/III), evaluated weekly doses of 25 mg, 50 mg, 100, 200 mg and 250 mg. This is discussed in detail in the section *Clinical efficacy, Pivotal or main efficacy studies* below.

5.4. Evaluator's conclusions on dose finding for the pivotal studies

Data from Study 045 indicated that administration of 25 mg (for each loading and weekly dose) did not provide sufficient protection in semi-immune African subjects. In contrast, protection with 50 mg, 100 mg, and 200 mg was similar to each other and to the mefloquine comparator, for the semi-immunes in this study. PE for the 200 mg based regimen was 86%, the same as the protective efficacy for mefloquine, the standard of care.

6. Clinical efficacy

For prophylactic studies, the subjects do not have disease, prior to accrual into the study. For malaria prophylactic studies, subjects are either healthy volunteers (when studies are performed on persons who do not live in the endemic region) or individuals who are healthy other than having asymptomatic parasitemia which is cured with standard malaria treatment agents before the subject is randomised to a study treatment group (when studies are performed in the endemic regions on local populations). The baseline health characteristics in these field studies are representative of the general population who will utilise anti-malarial prophylaxis with tafenoquine.

For the indication 'prophylaxis of malaria' post exposure, subjects received malaria prophylaxis or treatment with a standard agent in the endemic area, and then upon exiting the endemic region were randomised to post-exposure anti-hypnozoite prophylaxis with either standard primaquine or tafenoquine (Study 049).

The primary efficacy endpoint and primary efficacy analytic endpoints are based the cumulative incidence of parasitemia, with incidence density (parasitology per unit time) being used for secondary analyses, in conformity with the FDA Guidance document[3].

6.1. Studies providing evaluable efficacy data

The pivotal efficacy trial in this submission is Study 033, a Phase III, randomised, double blind, comparator controlled prophylactic trial in non-immunes to evaluate the anticipated clinical regimen of tafenoquine in comparison with mefloquine for the prophylaxis of Pf and Pv malaria in non-immune Australian soldiers deployed to East Timor (now Timor-Leste). Study 045 was

added as a second 'pivotal' study to show efficacy in 'semi-immunes' living in a malaria endemic area of Ghana.

For 'Prevention of Malaria while in the endemic region', the sponsor's designated key trials consist of at least one study with each of the above FDA recommended designs.

- Study 033: Active comparator controlled prophylactic trial in non-immunes returning from an endemic area.
- Study 045: A Phase II/III placebo controlled prophylactic trial in semi-immunes. This was a randomised, double blind, placebo controlled evaluation of tafenoquine compared to mefloquine for chemoprophylaxis in northern Ghana. One of the regimens was the anticipated clinical regimen.
- Study 043: Placebo controlled prophylactic trial in semi-immunes in Africa. One of the regimens was the anticipated clinical regimen.
- Study TQ-2016-02: A Phase II/III placebo controlled prophylactic study versus Pf in non-immunes in a human challenge model.
- Study 058: A Phase II/III treatment study of Pv in semi-immune Thai nationals, which also produced prophylaxis data.

Other studies that preceded and are submitted to support the key trials listed above consist of the following:

- Studies 053 and 054: Prophylactic efficacy of single dose (Study 053) and early multiple dose (Study 054) tafenoquine regimens in the human Pf challenge model.
- Study 006: Different loading doses for semi-immunes in Africa.
- Study 044: 'Full prophylactic regimen' with a higher dose than the final clinical dose for non-immunes in South East Asia.
- Study TAF-112582: A treatment/prophylaxis study in patients with Pv malaria in endemic areas.
- Study 030: The anticipated clinical regimen (200 mg per day x 3 days followed by 200 mg weekly) compared to placebo and positive control (mefloquine).

For the part of the indication 'Prophylaxis of malaria after leaving the endemic region', 5 relevant studies have been submitted. Pivotal Study 033 fulfils regulatory criterion - a comparison of tafenoquine to an active comparator (primaquine) in non-immunes. Supporting Study 049 also compares tafenoquine to primaquine in non-immunes. Supporting Studies 047 and 058 compare tafenoquine to primaquine in Thais who are of mixed immunity. Study 046 was an open label study.[5].

- Study 033: Upon exit of non-immunes from the endemic region, mefloquine subjects received primaquine while tafenoquine subjects were not further treated, thus permitting a comparison between primaquine and tafenoquine for post-exposure prophylaxis.
- Study 058: In addition to evaluating the treatment effect of tafenoquine against Pv already present in the blood of semi-immune Thai people, follow-up was extended to 120 days and thus assesses relapse of the tafenoquine regimen used compared to primaquine up to that time.
- Study 047: Wide range of short tafenoquine regimens compared to primaquine for Thais in South East Asia.

[5] Sponsor clarification: Study was suspended after initial vortex keratopathy findings were identified in Study 033. The study was not reopened.

- Study 049: Several short tafenoquine regimens compared to primaquine for Australian non-immunes.

For tafenoquine efficacy studies, males (3,232 subjects) predominated overall; however, 771 females also participated. The mean age of 29 years, the mean weight of 69 kg and the mean body mass index (BMI) of 23 signified a healthy young adult population. Subjects ranged in age from 12 years to 70 years. Drop-outs were few (approximately 2.5%).

The primary efficacy *endpoint* in all clinical trials was confirmed parasitaemia. Confirmed parasitaemia signifies that the presence of parasites in the blood smears had to be confirmed by two independent microscopists. The primary efficacy analytic parameter (the primary efficacy variable that was calculated from the parasitaemia data) in studies that contained a placebo group (Studies 006, 043, 044, 045, 030) was 'Protective Efficacy.' Protective efficacy versus placebo (PE) was defined as follows: PE = (attack rate of placebo – attack rate of tafenoquine) / (attack rate of placebo) = (1 - relative risk of developing parasitemia tafenoquine: placebo) x 100%. Where attack rate = number of subjects who developed parasitaemia / number of subjects. The primary efficacy analytic parameter in studies that did not contain a placebo group (Studies 033, 047, 049, and 058) was 'parasitaemia' or 'no-parasitaemia,' or the synonymous terms 'prophylactic failure' or 'prophylactic success'.

6.2. Pivotal or main efficacy studies

6.2.1. Study 033

6.2.1.1. Study design, objectives, locations and dates

Study 033 was a double blind, Phase III clinical trial conducted to evaluate the safety, tolerability, and efficacy of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune soldiers deployed to an endemic malarial area. Study 033 compared tafenoquine with mefloquine for the prophylaxis of both Pf and Pv malaria in healthy non-immune Australian soldiers deployed to East Timor (now Timor-Leste). The study was carried out at the Lavarack Barracks, Townsville, Australia and in East Timor (at seven sites). The study was divided into two phases. It was conducted between October 2000 and17 May 2001. Phase I consisted of a 26 week period during deployment where subjects received prophylactic. At the end of the deployment to the malarious area and once the subjects had returned to barracks in Townsville, Australia, the subjects entered a 24 week relapse follow-up phase (extended to 1 year). During this follow-up phase, subjects who had been on mefloquine prophylaxis received 14 days of primaquine (15 mg BID) while subjects on tafenoquine prophylaxis received placebo capsules for 14 days. The study was conducted at eight sites in Timor-Leste. Participants (N = 654).

Objectives

The primary study objective was to compare the safety and tolerability of tafenoquine and mefloquine during a 6 month period of treatment.

The secondary study objectives were:

- To assess the effectiveness of tafenoquine and mefloquine for chemoprophylaxis of Pf and Pv
- To assess the effectiveness of tafenoquine and primaquine in preventing post exposure malaria
- To characterise the population PK of tafenoquine and evaluate the effects of various subject characteristics on tafenoquine PK.

6.2.1.2. Inclusion and exclusion criteria

Healthy Australian soldiers, able to consent, no known glucose-6-phosphate dehydrogenase deficiency (G6PDD) as defined by Medical Class 1 or 2 (Australian Army standard), male or female and aged between 18 and 55 years inclusive.

Subjects with demonstrated G6PDD, a history of allergy or intolerance to study medication, a history of psychiatric disorders and/or seizures, or a history of drug or alcohol abuse were excluded. In addition, subjects with clinically significant medical history, concurrent conditions, or laboratory test results were also to be excluded.[6]

6.2.1.3. Study treatments

The first or prophylactic as above, study medication (tafenoquine 200 mg or mefloquine 250) in a ratio of 3:1. A loading dose of tafenoquine 200 mg for 3 days, followed by weekly tafenoquine 200 mg (n=492); or to daily loading dose of mefloquine 250 mg for 3 days, followed by weekly mefloquine 250 mg, (n = 162)) for the duration of the prophylactic phase. Samples for PK analysis were collected in windows on study Day 2 (1 to 12 hours post-final loading dose), 1 to 12 hours and 72 to 120 hours post weekly dose and pre dose for study Weeks 4, 8, 16, and 26 of the prophylactic phase.

6.2.1.4. Efficacy variables and outcomes

The primary efficacy endpoint was prophylactic failure: parasitologic and clinical failure during the 26 week prophylactic phase. The protocol defined principal efficacy analysis was based on the per-protocol (PP) population, all randomised subjects who satisfied inclusion/exclusion criteria and subsequently adhered to the protocol.

The secondary efficacy variables analysed were:

- Number of subjects experiencing clinical malaria at any time during the study (prophylactic phase plus 6 months relapse Follow-up phase);
- Number of subjects with a single positive smear (any species, with or without clinical signs/symptoms) during prophylactic study drug administration;
- Time to clinical malaria (all species) at any time during the study (prophylactic phase plus six months relapse Follow-up phase);
- Time to single positive smear (all species) with or without clinical signs/symptoms during prophylactic study drug administration.

6.2.1.5. Randomisation and blinding methods

This was done centrally.

6.2.1.6. Analysis populations

The principal efficacy analysis of Study 033 was based on the PP population, group and then the intention-to-treat (ITT) population was used to confirm the findings of the principal confirmatory analysis, under the following definitions:

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

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

[6] Sponsor comment: The reason for psychiatric disorder/seizure exclusions was because of mefloquine. Prior tafenoquine studies with no mefloquine as an active comparator had no such exclusions.

6.2.1.7. Sample size

It was calculated that in order to allow comparisons of safety to be made between tafenoquine and mefloquine given over 6 months, with a reasonable precision, at least 450 tafenoquine and 150 mefloquine subjects would need to complete the 6 months prophylactic phase. Approximately 5% of subjects randomised were expected to drop out, so 632 subjects were to be randomised in a 3:1 ratio; that is, with 474 subjects in the randomised to tafenoquine group and 158 subjects in the mefloquine group.

6.2.1.8. Statistical methods

Principal Analysis (PP Population): Treatment groups were compared for prophylactic outcome by calculating the difference in the proportion of prophylactic failures (tafenoquine-mefloquine) with a 95% CI. The CI was calculated for the difference in two binomial proportions using standard normal approximation theory. A conclusion of non-inferiority of tafenoquine was to be drawn if the upper limit of the Cl was no more than 10%.

Confirmatory Analyses: These were carried out using (i) ITT population and (ii) a worst case analysis in which subjects withdrawing during the prophylactic phase were included as failures.

Analysis of Secondary Efficacy Variables: For secondary variables involving numbers of subjects, treatment differences in proportions with 95% CIs were calculated.

6.2.1.9. Participant flow

The number of withdrawals was low in both treatment groups (< 5%) as shown in Table 20. There were no withdrawals due to prophylactic failure during the prophylactic phase. The proportion of subjects withdrawn due to AEs was similar in both treatment groups (2.4-2.5%).

Table 20: Subject disposition and demographic data (Study 033)

Population	Treatment group		
	Tafenoquine 200 mg	Mefloquine 250 mg	Total
Screened	–	–	663
Randomized	492	162	654
Safety population	492	162	654
Intent-to-treat population	492	162	654
Per protocol population	462	153	615

6.2.1.10. Major protocol violations/deviations

In the prophylactic phase, > 98% of subjects were compliant with study medication; 99.8% in the tafenoquine group and 98.8% in the mefloquine group. The majority of subjects (334/492 (67.9%) in the tafenoquine group and 107/162 (66%) in the mefloquine group) took their last dose on the day they left East Timor. Most of the remaining subjects (142/492 (28.9%) in the tafenoquine group and 49.162 (30.2%) in the mefloquine group) took their last dose within 3 days of leaving east Timor. Following the prophylactic phase, > 96% of subjects in both treatment groups were compliant with primaquine eradication medication or placebo.

6.2.1.11. Baseline data

As expected from this military population, the majority of subjects in all analysis groups were young White males. The majority of subjects in the study were male; 478/492 (97.2%) in the tafenoquine group and 154/163 (95.1%) in the mefloquine group. The mean age was 25.4 years in the tafenoquine group and 26.0 years in the mefloquine group. The overall age range was 18 to 51 years. The majority of subjects (> 98%) were White, with < 1% subjects in each group of Australian Aboriginal or Pacific Islanders.

Overall, 2.5% to 3% of tafenoquine and mefloquine treated participants had a history of malaria, with 0.6% to 1.8% reporting an attack in the preceding 6 months. All participants were healthy at the start of the study.

6.2.1.12. Results for the primary efficacy outcome

No subject was a prophylactic failure during the prophylactic phase. Historic control data indicate that 7.9% of subjects would have become infected (6.9% with Pv; 1.0% with Pf) under those conditions. The ITT population was used to confirm the findings of the principal analysis. No subjects in either treatment group developed malaria during the prophylactic phase of the study, as shown in Table 21.

Table 21: Prophylactic outcome by treatment group, prophylactic phase (Study 033)

Population	Per protocol population		Intent to treat population	
	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine
	N = 462	N = 153	N = 490	N = 161
Prophylactic success (total) Prophylactic success (known)	462 (100%) 462 (100%)	153 (100%) 153 (100%)	490 (100%) 473 (96.5%)	161 (100%) 157 (97.5%)
Prophylactic success (assumed)	0	0	17 (3.5%)	4 (2.5%)
Prophylactic failure	0	0	0	0

'Assumed success' defined as no malaria during participation in the study for subjects withdrawn during prophylactic phase. N: number.

6.2.1.13. Results for other efficacy outcomes

A worst case analysis was performed assuming that all subjects who withdrew from the study were failures. In this analysis, the prophylactic success rate was > 96% in both treatment groups, with no difference between the groups.

In the 24 week follow up phase after leaving the endemic region, and after receiving no further drug (tafenoquine group), or standard post-exposure prophylaxis with primaquine, there were four cases of Pv malaria in the tafenoquine group and one case of Pv malaria in the mefloquine group. The failure rate due to Pv relapse was 0.9% for the tafenoquine group and 0.7% for the primaquine group. The time to relapse after the last dose of tafenoquine or mefloquine was 12-20 weeks for the four tafenoquine failures and 12 weeks for the one mefloquine, then primaquine failure. When the observation period was extended to 1 year, there were 3 more failures in the tafenoquine group and one in the mefloquine/primaquine group. This difference did not however reach statistical significance.

The data from the relapses was used to try to calculate a theoretical attack rate from the exposure period.[7] From this a study re-evaluation was conducted. In a retrospective analysis of the trial results, a conservative malaria attack rate of 7.88% was estimated based on prior malaria attack rate data in the previous wet seasons amongst ADF soldiers and breakthrough incidences of Pv in the 12 months following the study. Based on the 7.88% estimated attack rate, the protective efficacy (PE) of tafenoquine and mefloquine (with corresponding 95% CI) were determined to be 100% (93%, 100%) and 100% (79%, 100%) respectively. This led to the conclusion that the PE of tafenoquine (200 mg per day for 3 days, followed by weekly 200 mg maintenance doses) was similar to that of the weekly standard of care (mefloquine, 250 mg) observed in both Study 033 and the results of tafenoquine studies in which placebo controls could also be used.[8]

[7] Sponsor clarification: The study was active controlled, and a placebo group would have been unethical in deployed, non-immune military personnel.

[8] Sponsor clarification: That is, semi-immune persons from countries with endemic malaria.

6.2.1.14. Evaluator commentary

In non-immunes, while in the endemic region, the proposed tafenoquine prophylactic regimen had efficacy similar to that of the active comparator drug, mefloquine, no subject had parasitaemia in either group over 6 months of prophylaxis. Historic control data (provided by the sponsor) indicate that a conservative value of 7.9% of subjects would have become infected (6.9% with Pv, 1.0% with Pf) under those conditions. Statistically from the data in this study, tafenoquine is non-inferior to mefloquine. This study was just large enough for these numbers (with high compliance and low dropout rate) to reach significance. It is however, quite small as the pivotal efficacy study for the major justification for licensing of this drug in Australia (prophylaxis in non-immunes).

6.2.2. Study 045

6.2.2.1. Study design, objectives, locations and dates

This was a randomised, double blind, placebo controlled evaluation of increasing doses of weekly tafenoquine for chemo-suppression of plasmodium falciparum in semi-immune adults living in Northern Ghana. Subjects who met the entry criteria were given a three day presumptive course of halofantrine to eliminate any existing Plasmodium parasitemia. Subjects were then randomised into one of four groups to receive one of three dosage regimens of tafenoquine or a placebo regimen for 10 to 15 weeks. There was an additional four weeks of Follow-up after the end of drug administration. Subjects were evaluated for Plasmodium parasitaemia by weekly blood smears and evaluated for tolerability and safety by questioning and periodic blood tests. The study objectives were: (i) To determine the chemosuppressive efficacy of weekly tafenoquine at a range between 25 and 200 mg in preventing Pf parasitaemia compared to placebo, and secondarily to mefloquine, in subjects semi-immune to malaria, and (ii) To establish the minimum effective prophylactic dose of weekly tafenoquine and to assess the tolerability of that dose. The first subjects were screened for the study on 13 August 1998, the first loading dose was given on 15 September 1998 and the last dose of prophylaxis medication was given on 27 December 1998.

6.2.2.2. Inclusion and exclusion criteria

Subjects included were consenting G6PD-normal adults between 18 to 60 and 55 years of age, female subjects aged 50 to 60 were eligible for entry to the study if they were in good general health and planned to stay in the study area until the end of the study.

6.2.2.3. Study treatments

Subjects received a radical cure regimen of quinine (10 mg/kg three times daily) for four days followed, on the fifth day, by a 7 day course of doxycycline (100 mg by mouth bid) and a 14 day course of primaquine (30 mg daily). Subjects then received a loading dose of tafenoquine (25, 50, 100 or 200 mg), mefloquine (250 mg), or placebo daily over three days, followed by weekly dosing with the same medication. Five (5) days were left between completion of the radical cure regimen and initiation of randomised study medication. A snack was given to all subjects prior to ingestion of each dose of medication.

6.2.2.4. Efficacy variables and outcomes

The primary outcome was to determine the chemosuppressive efficacy of weekly tafenoquine at a range between 25 and 200 mg in preventing falciparum parasitaemia compared to placebo, and secondarily to mefloquine in subjects that were semi-immune to malaria. Secondary efficacy parameters were the time to the first positive smear, the PE was derived from the proportion of subjects who were based on 'confirmed' parasitaemia (two consecutive positive smears), time to confirmed chemoprophylactic failures that is, developed confirmed parasitaemia at any time during the double blind prophylaxis phase.

6.2.2.5. Randomisation and blinding methods

Randomisation was done electronically and all study treatments were identical. Both participants and investigators were blinded.

6.2.2.6. Analysis populations

Two populations were defined as follows for the analyses of efficacy. The full data set, based on the principle of intent-to-treat, was the primary data set. This comprised data from all subjects who were randomised to receive any of the study medications and received at least one dose of weekly prophylactic medication, and who had at least one efficacy assessment. The PP data set was used for a supplementary analysis. This comprised data from all subjects fully compliant with the study protocol who received the full course of treatment, unless they were withdrawn from randomised medication prematurely as a result of developing parasitaemia.

6.2.2.7. Results for the primary efficacy outcome

The ITT efficacy population comprised subjects who received all clearance and loading medication and who received at least one dose in the weekly dosing regimen. Efficacy analyses were evaluated using the efficacy population, which comprised subjects in the ITT efficacy population who provided at least one on-therapy malarial blood smear.

6.2.2.8. Sample size

In total, 868 subjects were screened for entry to the study. The allocation to groups is shown in Table 22.

Table 22: Subject disposition (Study 045)

Population Number of subjects	Treatment Group						Total
	Placebo	TQ 25 mg	TQ 50 mg	TQ 100 mg	TQ 200 mg	MQ 250 mg	
Screened	-	-	-	-	-	-	868
Started radical cure	-	-	-	-	-	-	531
Randomized	96	95	94	94	94	48	521
Completed radical cure	96	95	94	94	93	48	520
Started loading dose*	94	93	93	94	93	46	513
Full data set	94	93	91	94	91	46	509
Per protocol data set	83	83	74	80	68	40	428
Completed prophylaxis phase	24	60	78	86	76	44	368

6.2.2.9. Statistical methods

The PE for each dose of tafenoquine relative to placebo was calculated using the observed values at each dose and placebo; similarly for the PE of mefloquine. The CI for the estimates of PE was derived using the method described by Koopman. A logistic regression analysis was used to determine the dose response for the probability of prophylactic success over the range of doses in the study. The time to first occurrence of malaria and the time to confirmed parasitaemia were calculated using Kaplan-Meier survival methods.

6.2.2.10. Participant flow

A total of 521 subjects were randomised to one of the treatment groups and allocated a study number; eight of these subjects, however, were randomised in error and did not receive the loading dose. Thus 513 subjects started the loading dose of therapy in the prophylaxis phase of the study, but four of these subjects were excluded from the full data set because they did not start weekly dosing and no efficacy data were available. Subject disposition is shown in Table 23.

Table 23: Subject disposition (Study 045)

Population Number of subjects	Treatment Group						Total
	Placebo	TQ 25 mg	TQ 50 mg	TQ 100 mg	TQ 200 mg	MQ 250 mg	
Screened	-	-	-	-	-	-	868
Started radical cure	-	-	-	-	-	-	531
Randomized	96	95	94	94	94	48	521
Completed radical cure	96	95	94	94	93	48	520
Started loading dose*	94	93	93	94	93	46	513
Full data set	94	93	91	94	91	46	509
Per protocol data set	83	83	74	80	68	40	428
Completed prophylaxis phase	24	60	78	86	76	44	368

6.2.2.11. Major protocol violations/deviations

In the placebo group only 25.5% of subjects completed the study and in the tafenoquine 25 mg group 64.5% of subjects completed the study. Most of the withdrawals in these groups were due to subjects developing parasitaemia. There were only three withdrawals as a result of parasitaemia in the other tafenoquine groups and none in the mefloquine group. The proportions of subjects discontinued for AEs or non-compliance were 8.5% in the placebo group, 7.5% to 15.4% in the tafenoquine groups and 4.3% in the mefloquine group.

6.2.2.12. Baseline data

Baseline data was similar amongst groups and is shown in Table 24.

Table 24: Demographic characteristics of the Study 045 population

Demographic Characteristic	Treatment Group					
	Placebo	TQ 25 mg	TQ 50 mg	TQ 100 mg	TQ 200 mg	MQ 250 mg
	N = 94	N = 93	N = 91	N = 94	N = 91	N = 46
Sex, n (%) Male	62 (66.0%)	55 (59.1%)	57 (62.6%)	67 (71.3%)	59 (64.8%)	33 (71.7%)
Female	32 (34.0%)	38 (40.9%)	34 (37.4%)	27 (28.7%)	32 (35.2%)	13 (28.3%)
Age (years) males Mean	39	40	36	38	39	37
Median	40	40	36	38	38	35
Range	17 - 60	14 - 63	18 - 58	18 - 60	18 - 63	19 - 58
Age (years) females Mean	53	53	53	53	54	52
Median	53	54	54	54	54	53
Range	46 - 60	45 - 59	38 - 59	46 - 60	46 - 69	45 - 59

6.2.2.13. Results for other efficacy outcomes

Primary efficacy variables: The incidence of parasitaemia (that is, the proportions of subjects with at least one positive blood smear) and the PE based on first positive smear during prophylaxis treatment is summarised in Table 25 for the full data set. In the placebo group, 91.5% of subjects had a positive smear within the 13 weeks of observation. Although some protection was offered by tafenoquine at a dose of 25 mg, the greatest protection was afforded by the three highest doses of tafenoquine, which all provided a PE of between 84% and 87%, similar to that provided by mefloquine. In the per protocol analysis, results were similar to those in the full data set.

The analysis of the tafenoquine dose-response relationship indicated that there was a significant interaction with weight and log dose ($p < 0.001$). The interaction with weight was caused primarily by the high incidence of positive smears amongst heavier subjects in the lowest dose group.

Table 25: Parasitaemia and protective efficacy (Study 045)

Parasitemia	Treatment Group					
	Placebo	TQ 25 mg	TQ 50 mg	TQ 100 mg	TQ 200 mg	MQ 250 mg
	N = 94	N = 93	N = 91	N = 94	N = 91	N = 46
No. with positive smear	86	58	13	11	12	6
Incidence (%)	91.5	62.4	14.3	11.7	13.2	13.0
PE (%)	-	31.8	84.4	87.2	85.6	85.7
95% CI for PE	-	20.2, 43.4	74.8, 90.7	78.3, 92.7	76.2, 91.6	71.9, 93.3

6.2.2.14. Results for other efficacy outcomes

Secondary efficacy variables: In the placebo and low dose tafenoquine groups, a majority of subjects (83.7% and 58.6%, respectively) who developed positive smears did so within 6 weeks of starting randomised medication. The median time to first positive smear could not be calculated for the three highest tafenoquine dose groups and the mefloquine group because more than 50% of subjects in these groups had no positive smears. In the full analysis set, the median time to first positive smear in the placebo group was 31 days, and in the tafenoquine 25 mg group was 53 days.

For confirmed parasitaemia (based on two consecutive positive smears), there were no subjects in the two highest tafenoquine dose groups or in the mefloquine group and the incidence in the tafenoquine 50 mg and 25 mg groups were 2.2% and 28.0% respectively. These results compare with a placebo incidence of confirmed parasitaemia of 64.9%. This resulted in PEs based on confirmed parasitaemia of 100% in the tafenoquine 100 mg and 200 mg groups and the mefloquine group in this semi-immune population.

Analysis of incidence density demonstrated a placebo attack rate of approximately nine attacks per person per year, compared with slightly less than four attacks per person per year on the 25 mg dose of tafenoquine and less than one attack on the tafenoquine doses of 50 to 200 mg or 250 mg dose of mefloquine.

6.2.2.15. Evaluator commentary

Doses of 50 mg, 100 mg, and 200 mg tafenoquine provided effective prophylaxis in an area of intense Pf transmission, with PE relative to placebo of 84% to 87% over the 13 week assessment period, values similar to those obtained with mefloquine. The 200 mg dose was equivalent to standard of care.[9]

6.2.3. Study 043

6.2.3.1. Study design, objectives, locations and dates

This study was a placebo controlled randomised, double blind, parallel group, and single centre study in subjects living in an area of holoendemic Pf malaria transmission. It was conducted to

[9] Sponsor comment: There are arguments that tafenoquine should have been compared to mefloquine. This is impractical, in field studies at the time: 1) Malarone was not a licenced chemoprophylactic comparator at the time; 2) Malarone must be taken daily and blinding would have been quite difficult, even though compliance with two causal drugs would have separated out the effects in a large enough population.

evaluate weekly tafenoquine compared to placebo for chemo-suppression of *Plasmodium falciparum* in Western Kenya. This study was conducted at one site between 17 May 1997 and 29 September 1997 and was the first 'in the field' proof of concept study. The primary objectives were to determine the chemosuppressive effectiveness of weekly regimens of tafenoquine in preventing falciparum parasitemia compared with placebo.

Subjects who met the entry criteria were given a three day presumptive course of halofantrine to eliminate any existing *Plasmodium* parasitemia. Subjects were then randomised into one of four groups to receive one of three dosage regimens of tafenoquine or a placebo regimen for 10 to 15 weeks. There was an additional four weeks of Follow-up after the end of drug administration. Subjects were evaluated for Plasmodium parasitaemia by weekly blood smears and evaluated for tolerability and safety by questioning and periodic blood tests.

6.2.3.2. Inclusion and exclusion criteria

Subjects included were consenting, G6PD-normal adults between 18 and 55 years of age, in good health and living in Kenya.

6.2.3.3. Study treatments

Subjects completed an initial course of halofantrine, 250 mg daily for 3 days with food, as a curative course of antimalarial treatment to clear pre-existing parasitaemia before prophylaxis. Subjects were then randomised to one of the following treatment groups:

a. Tafenoquine load only: 400 mg of tafenoquine for 3 days followed by placebo for up to 15 weeks.

b. Tafenoquine low dose: 200 mg of tafenoquine for 3 days, followed by tafenoquine 200 mg weekly for 15 weeks.

c. Tafenoquine high weekly dose: 400 mg of tafenoquine for 3 days followed by tafenoquine 400 mg weekly for 15 weeks.

d. Placebo: Weekly medication schedule was identical to the above tafenoquine schedule except that no active drug was contained in the capsules.

6.2.3.4. Efficacy variables and outcomes

The primary efficacy parameter was PE of the three tafenoquine regimens relative to placebo. The PE was derived from the proportion of subjects who were chemoprophylactic failures that is, developed confirmed parasitaemia at any time during the double blind prophylaxis phase. Confirmed parasitaemia was defined as having occurred when a subject had two consecutive blood smears positive for Plasmodia, read independently by two microscopists blinded to one another's diagnosis.

Other outcomes include safety parameters and pharmacokinetics and parasite drug sensitivity.

6.2.3.5. Randomisation and blinding methods

Participants were randomised and given numerated treatment packs.

6.2.3.6. Analysis populations

Subjects were included in the summaries of safety if they had entered the study, completed the clearance phase, and taken at least one dose of tafenoquine during the loading phase (safety population). The ITT efficacy population comprised subjects who received all clearance and loading medication and who received at least one dose in the weekly dosing regimen. Efficacy analyses were evaluated using the efficacy population, which comprised subjects in the ITT efficacy population who provided at least one on-therapy malarial blood smear.

6.2.3.7. Sample size

The original plan was to enrol 300 adults to obtain 240 completed subjects (60 per treatment group).

6.2.3.8. Statistical methods

The original analysis for the study considered all cases of confirmed parasitaemia up to and including the date of last dose of study medication, as a failure of prophylaxis. The majority of the analyses were conducted in this way, although whilst the study was being reported, after the Phase III program was undergoing design, a number of additional analyses were performed in order to facilitate some limited comparisons between Phase II and Phase III data.

6.2.3.9. Participant flow

Of the 249 consenting subjects from the study area who were randomised into one of the four treatment groups, 235 (94%) received the clearance regimen and went on to receive at least one loading dose of study medication (safety population), 229 (92%) received all three loading doses and at least one dose of the weekly study medication (ITT efficacy population), and 223 (90%) gave a blood sample for a malaria smear after receiving a weekly dose and were evaluable for efficacy (efficacy population).

6.2.3.10. Major protocol violations/deviations

No details provided in the study report, apart from 2 discontinuations due to AEs (one haemolytic anaemia requiring hospitalisation).

6.2.3.11. Baseline data

The demographic data were generally similar in the four treatment groups, although in all the individual treatment groups and the study as a whole there were more men (61%) than women (39%). The mean age of subjects was 32.5 years with a range from 17 to 55.

6.2.3.12. Results for the primary efficacy outcome

The proportion of subjects with confirmed parasitaemia was substantially lower in subjects who received tafenoquine compared to those on placebo. Subjects were not withdrawn from the study unless the parasitaemia was symptomatic and required therapy. During the prophylactic treatment period, the total number of subjects developing confirmed parasitaemia was 79 (35%). All infective episodes except one were due to Pf, the single non-falciparum case being due to Pm (in the load only group). The proportion of subjects developing confirmed parasitaemia in the placebo group during the treatment period was 92%, confirming this as being a region of intense Pf transmission. By comparison, the proportion of subjects during the study developing confirmed parasitaemia in the three tafenoquine treatment groups was markedly lower at 26% for load-only, 11% for low dose and 9% for high dose groups. The corresponding protective efficacies (95% C.I) were 71.7% (57.0, 82.5), 87.6% and 90.4% (79.2, 95.9) respectively.

The original analysis planned for the study considered all cases of confirmed parasitaemia up to and including the date of last dose of study medication as a failure of prophylaxis. The principal analysis was performed on the full data set and the PP data set was used for a confirmatory analysis and is shown in Table 26.

Table 26: Efficacy parameters, original analysis; protective efficacy (Study 043)

	Treatment Group			
	Placebo	Tafenoquine Load only (400 mg)	Tafenoquine Low Dose (200 mg)	Tafenoquine High Dose (400 mg)
	N = 59	N = 54	N = 53	N = 57
PRIMARY EFFICACY PARAMETER from third loading dose to end of study				
Confirmed Parasitemia	54 (92%)	14 (26%)	6 (11%)	5 (9%)
Protective Efficacy	–	71.7%	87.6%	90.4%
95% CI	–	(57.0, 82.5)	(75.2, 94.2)	(79.2, 95.9)
SECONDARY EFFICACY PARAMETER from third loading dose to 10 weeks				
Protective Efficacy	–	87.2%	89.1%	93.9%
95% CI	–	(74.1, 94.0)	(76.4, 95.3)	(83.3, 97.9)
SECONDARY EFFICACY PARAMETER from third loading dose to 7 weeks				
Protective Efficacy	–	91.1%	–	–
95% CI	–	(72.9, 99.5)	–	–

A reanalysis of PE was performed to reflect the methodology of the Phase III clinical program (parasitaemia up to 7 days after last study dose). Additionally, PE was recalculated using incidence density, which takes into account the duration of exposure to infection of study subjects. Results of the reanalysis are summarised in Table 27 below and are broadly reflective of the original analysis. At the end of prophylaxis, the protective efficacy using the modified analysis was comparable in all groups, just 2-3% lower than in the original analysis; 67.6% (52.5, 79.2) in load-only, 85.6% (72.7, 92.9) in low dose and 88.5% (76.8, 94.6) in high dose groups respectively.

6.2.3.13. Results for other efficacy outcomes

Other efficacy outcome results are shown in Table 27 below.

Table 27: Efficacy parameters, reanalysis; protective efficacy (Study 043)

	Treatment Group			
	Placebo	Tafenoquine Load only (400 mg)	Tafenoquine Low Dose (200 mg)	Tafenoquine High Dose (400 mg)
	N = 59	N = 54	N = 53	N = 57
From first loading dose to end of the study – cumulative incidence of parasitemia				
Confirmed Parasitemia	54 (92%)	16 (30%)	7 (13%)	6 (11%)
Protective Efficacy	–	67.6%	85.6%	88.5%
95% CI	–	(52.5, 79.2)	(72.7, 92.9)	(76.8, 94.6)
From first loading dose to 7 weeks – cumulative incidence of parasitemia				
Protective Efficacy	–	81.8%	81.4%	89.6%
95% CI	–	(59.0, 92.3)	(58.3, 92.2)	(70.8, 96.5)
From first loading dose to end of the study – incidence density of parasitemia				
Protective Efficacy	–	79.5%	91.1%	93.2%
95% CI	–	(64.2, 88.3)	(80.5, 96.0)	(84.2, 97.1)

6.2.3.14. Evaluator commentary

Tafenoquine was demonstrated to be effective as prophylaxis against Pf infections in this semi-immune subject population. Using a three day loading plus weekly dosing regimen of tafenoquine, PE relative to placebo of 85% to 89% were obtained on 200 mg and 400 mg of tafenoquine over the median 12 week treatment period of the study. This study also found that a 3 day loading dose of 400 mg tafenoquine provided good protection against Pf infection for a period of up to seven weeks after dosing.

6.2.4. Study TQ-2016-02

6.2.4.1. Study design, objectives, locations and dates

This was a randomised, double blinded, placebo controlled study in healthy, non-immune adults to determine the schizonticidal activity of tafenoquine after challenge with Pf blood stage parasites. It was conducted between 12 January 2017 and 31 March 2017 in Australia. The primary objective was to evaluate the schizonticidal activity of tafenoquine administered orally against challenge with blood stage Plasmodium falciparum in healthy, non-immune participants.

Secondary objectives were to characterise the PK/PD relationship between tafenoquine concentration and Malaria Failure (defined as a participant with a quantitative polymerase chain-reaction (qPCR) parasitaemia of > 5,000 asexual blood stage parasites/mL accompanied by clinical symptoms; or, parasitaemia of > 5,000 asexual blood stage parasites/mL and increasing 2 fold within 48 hours), and to evaluate the safety and tolerability of tafenoquine in healthy, non-immune participants and following challenge with blood stage Pf.

The induced blood stage malaria challenge model was used to assess the schizonticidal activity of tafenoquine against challenge with blood stage Pf. The study population was comprised of 2 cohorts of 8 participants. Within each cohort, participants were randomised to receive tafenoquine or placebo in a 6:2 ratio. Data from both cohorts was pooled for the analysis by treatment group at the end of study (EOS). Participants received either tafenoquine 200 mg (two 125 mg tablets of tafenoquine succinate, each equivalent to 100 mg of free base) or placebo. Tafenoquine or placebo was administered once per day via the oral route to participants after their normal breakfast. This occurred for 3 consecutive days (Days 1- to 3, the 'loading dose') and was followed, 7 days later, by another 200 mg dose of tafenoquine or placebo (on Day 10). Participants returned to the Clinical Research Unit (CRU) on Day 13 and were inoculated intravenously with erythrocytes containing approximately 2800 viable Pf malaria parasites. Within each cohort, all inoculations occurred within 60 minutes of inoculation of the first participant, and all participants remained at the CRU for at least 60 minutes post inoculation for observation of any immediate adverse reactions. Thereafter, participants were monitored by telephone call on a daily basis from Day 14 to Day 16. Participants returned to the CRU for daily clinical evaluation and blood sampling for tafenoquine PK and qPCR assessment of parasitaemia. Assessment of parasitaemia occurred from Day 17 until the qPCR demonstrated positivity for malaria, or, if qPCR remained negative, until approximately Day 32.

Following demonstration of positivity by qPCR, participants were to attend twice daily visits to the CRU for clinical assessment and blood sampling for qPCR. If qPCR results were negative over a 48 hour period or <5000 asexual blood stage parasites/mL and stable, then subsequent qPCR sampling reverted to 3 times per week until commencement of Riamet treatment (20 mg artemether/120 mg lumefantrine), with scheduling made at the Investigator's discretion. The results of the clinical evaluation and qPCR were used to ascertain attainment of the treatment threshold for initiation of early Riamet therapy.

6.2.4.2. Inclusion and exclusion criteria

Healthy men and women aged 18 to 55 years, with no previous history of exposure to malaria infection.

6.2.4.3. Study treatments

The treatment group received tafenoquine 200 mg (two 125 mg tablets of tafenoquine succinate, each equivalent to 100 mg of free base) daily on Days 1 to 3, then again on Day 10. The control group received placebo.

All participants received a standard course of antimalarial therapy with Riamet on Day 32 or earlier in the event of Malaria Failure or at the discretion of the investigator. If required for clearance of gametocytes, Primacin (primaquine) 45 mg was to be administered as a single oral dose at the time of Riamet treatment.

6.2.4.4. Efficacy variables and outcomes

- The ability of tafenoquine to prevent symptomatic malaria and parasitemia in a controlled malaria challenge study.
- Secondary outcomes were PK and safety.

6.2.4.5. Randomisation and blinding methods

This was done electronically according to the randomisation plan.

6.2.4.6. Analysis populations

The following analysis populations were defined for the study:

- Safety population: All participants who received study treatment at least once or inoculum were included in the safety population. Participants were analysed as treated. This was the primary population for safety and tolerability analyses.
- ITT population (analysed as treated): The ITT population consisted of all randomised participants who received at least one dose of study treatment, the inoculum and those who had at least one post-inoculum evaluation from Day 20 to Day 34.
- PP population (analysed as treated): All participants who received study treatment from Days 1-3 and again at Day 10, who had baseline evaluations conducted on Day 1 prior to IMP administration, who received inoculum on Day 13 and completed all malaria monitoring visits from Day 17 to the EOS visit (Day 34 ± 2 days) and who had no major protocol deviations. This was the primary population for the primary efficacy endpoint analysis.

6.2.4.7. Sample size

- Sixteen healthy volunteers between 18-65 years.

6.2.4.8. Statistical methods

For categorical/discrete variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable was presented. Continuous variables were summarised using descriptive statistics, including n, mean, standard deviation (SD), median, minimum, and maximum values. Geometric mean and coefficient of variation (%CV) were included for PK parameters, where appropriate.

6.2.4.9. Participant flow

All participants completed the study.

6.2.4.10. Major protocol violations/deviations

None reported.

6.2.4.11. Baseline data

The study population was comprised of 2 cohorts of 8 participants each to facilitate the safety and the logistics of participant inoculation and sample analysis at the CRU.

6.2.4.12. Results for the primary efficacy outcome

Administration of a loading dose of 200 mg tafenoquine, once daily for 3 days, followed a week later by a 200 mg post-loading dose, was completely effective in preventing symptomatic blood-stage infection following inoculation of non-immune, healthy volunteers with approximately 2800 Pf blood stage parasites in the Induced Blood Stage Malaria (IBSM) challenge model. In contrast to the placebo group, tafenoquine treated participants remained clear of blood-stage parasites for the duration of the study[10]. Tafenoquine demonstrated significant schizonticidal activity in non-immune participants with no occurrences of malaria failure, compared to 100.0% malaria failure among participants administered placebo (Table 28). The observed difference in the proportion of participants experiencing malaria failure between the tafenoquine and placebo groups was highly statistically significant (Fisher's exact test p=0.0005). Based on no occurrences of malaria failure with tafenoquine, the PE of active treatment was determined to be 100.0 %.

Table 28: Efficacy results; Study TQ-2016-02

Statistics	Tafenoquine (N=12)	Placebo (N=4)
Malaria Failure (%)	0 (0.0%)	4 (100.0%)
95% CI for Malaria Failure Rate	0.0%, 26.5%	39.8%, 100.0%
p-value (Fisher's Exact Test)	**0.0005**	
Relative Risk	**0.00**	
Protective Efficacy	**100.0**	

The IBSM challenge model performed as expected with the predicted parasitaemia profile in all placebo participants following inoculation on Day 13. The clinical scores observed were consistent with the parasitaemia data. Evaluation of the signs and symptoms of malaria by the malaria clinical score in these symptomatic placebo participants reflected the observed parasitaemia profile in this treatment group, as detected by qPCR, both before and after rescue with Riamet.

6.2.4.13. Results for other efficacy outcomes

Not applicable.

6.2.4.14. Evaluator commentary

Administration of an oral tafenoquine loading dose of 200 mg once daily for 3 days, followed a week later by a 200 mg post-loading dose, was efficacious and well tolerated in this study population. The tafenoquine steady state drug concentrations achieved with the dosing regimen were completely effective (100.0% PE) against challenge with approximately 2800 Pf blood stage parasites in the IBSM model in healthy, non-immune adult participants. The results of this study suggest that after challenge in the field by Pf sporozoites, parasites that escape parasiticidal activity of tafenoquine in the liver will be killed by tafenoquine in the blood.

6.3. Other efficacy studies

6.3.1. Study 058

This study was conducted to evaluate the efficacy and safety of tafenoquine for the treatment of Pv in adults. It was conducted in one centre in Thailand between 16 September 2003 and

[10]Sponsor clarification: Undetectable by qPCR.

10 January 2005. The primary objective was to assess whether a single 600 mg dose or 400 mg/day for three days of tafenoquine alone could clear/cure Pv blood stage infections. The 600 mg dose was planned for Cohort 2 which never eventuated.

6.3.1.1. Secondary Objectives

- To assess whether a 400 mg/day for three days of tafenoquine alone could prevent Pv relapse for two, three, and four months.
- Determination of parasite, gametocyte, and fever clearance time (PCT, GCT and FCT).
- To establish the safety and tolerability of these doses of tafenoquine.
- To characterise the population PK of tafenoquine.

6.3.1.2. Methodology

This was a Phase II randomised, active-control, double blind, double dummy study to be conducted in two sequential cohorts. The primary endpoint of the study was not met, and Cohort 2 was abandoned.

A planned interim analysis was performed after all subjects in Cohort 1 had completed the Day 28 assessment and an IDMC convened to evaluate the efficacy and safety of the tafenoquine dosing regimen (400 mg tafenoquine once per day for 3 days) used in Cohort 1. Only if the results from Cohort 1 met pre-defined efficacy and safety criteria, was enrolment to begin for Cohort 2. The efficacy criterion for achieving the primary endpoint was that the lower limit of the one-sided 95% CI (that is, 2-sided 90%), was no less than 85%, and for safety that a review of trends in all AEs, tolerability, medical observations, methaemoglobin and other lab data for all subjects indicated the dose to be well tolerated.

Subjects enrolled into the study were hospitalised at the Bangkok Hospital for Tropical Diseases for the first 29 days of the study and were asked to remain in a malaria non-endemic area until 90 days after the start of the study for follow-up with scheduled assessments at Days 60 and 90. Subjects were contacted at Day 120 for a Follow-up blood smear. Subjects remained in the study for 121 days from start of treatment to end of routine Follow-up.

This study enrolled male and female subjects aged 20-60 years with confirmed Pv malaria, who were willing to be hospitalised for 29 days and remain in a malaria-free region for 60 days thereafter for Follow-up. Subjects with demonstrated G6PDD were excluded.

Subjects in Cohort 1 were randomised 2:1 to receive two tafenoquine capsules (200 mg base/capsule for a total of 400 mg base) for 3 days followed by 14 days of placebo or chloroquine 1000 mg x 3 days then primaquine 15 mg/day for 14 days.

The primary efficacy outcome was cure rate at Day 28. Secondary efficacy endpoints (prevention of relapse, GCT, and PCT) thick and thin blood smears for malaria were obtained by finger prick at Baseline (Day 0) and then every 12 hours up to and including Day 7, until the blood smear became negative. Parasites and gametocytes were considered cleared if two consecutive blood smears were negative. After Day 7, thick and thin blood smears were obtained once a day by finger prick on Day 14, Day 28, Day 60, Day 90, and Day 120. Participants were electronically randomised and given medication packs that were all identical,

Four populations were defined for the analysis of the data to be collected as part of this study.

ITT: all randomised subjects who received at least one dose of study medication (that is, tafenoquine or chloroquine/primaquine), regardless of whether the dose or re dose was vomited. 3 *PP Populations*: *Day 7 PP Population, Day 28 PP Population, and Day 90 PP Population*. Subjects in the ITT population were eligible for the various PP populations if they: completed all scheduled assessments, were compliant with study medication, had no major protocol violations.

Planned enrolment for this study for the two cohorts was 140 subjects. 70 to Cohort 1 followed by 70 to Cohort 2. From this sample size, the aim was to yield 120 evaluable subjects in total, with 60 subjects for each cohort. A 2:1 randomisation ratio was to be used to obtain 40 evaluable subjects in each of the two cohorts for the tafenoquine arm and 20 evaluable subjects in each of the two cohorts for the comparator arm.

The primary endpoint was the Day 28 cure rate. The primary interest for this study concerned the null hypothesis that a given dose of tafenoquine (that is, a single 600 mg dose or 400 mg/day for 3 days) was not efficacious in clearing/curing Pv blood stage infections. The alternative hypothesis was that the tafenoquine dose under study was efficacious in clearing/curing these infections. For each cohort, it was to be concluded that the dose of tafenoquine was efficacious if the lower bound of the two-sided 90% CI (to give a one-sided test, 5% error level) for the Day 28 cure rate for tafenoquine subjects in the cohort was no less than 85%.

Of the 46 subjects randomised to receive tafenoquine, 35 (76%) completed the study and in the chloroquine, of 24 randomised participants, 19 (79/%) completed it. There were no withdrawals due to AEs in the tafenoquine group (2 in the chloroquine/primaquine group) and 2 withdrawals due to lack of efficacy in the tafenoquine groups (1 in the chloroquine group). This is shown in Table 29.

The groups were similar in all demographics. These are shown in Table 30. The primary and secondary efficacy results are summarised in Table 31 and 32. In terms of PP participants with an adequate clinical response, this was 93% 90% CI: 82.9, 98.1) and 100% (CI: 87.3, 100.0) in the tafenoquine and control groups respectively.

During its review, the IDMC determined that the dosing regimen of tafenoquine used in Cohort 1 failed to meet the pre-specified endpoint for the Day 28 cure rate due to three early treatment failures. The IDMC also determined that tafenoquine by itself was significantly worse in terms of parasite clearance time (mean parasite clearance time in the PP group was 82.5 hours versus 40.0 hours) and significantly slower in fever clearance time than chloroquine plus primaquine (41.1 hours versus 24.7 hours). The IDMC recommended enrolment into Cohort 2 should not be initiated and Follow-up in Cohort 1 should be completed according to the protocol. Following last subject last visit for Cohort 1 the study was terminated. Results for other efficacy outcomes are shown in Table 33.

Table 29: Participant flow (Study 058)

Number of Subjects	TQ	CQ + PQ
Planned Cohort 1, N	46	24
Randomized, N	46	24
Completed, n (%)	35 (76.1%)	19 (79.2%)
Total Number Subjects Withdrawn, n (%)	11 (23.9%)	5 (20.8%)
Withdrawn due to Adverse Events, n (%)	0	2 (8.3%)
Withdrawn due to Lack of Efficacy, n (%)	2 (4.3%)	1 (4.2%)
Withdrawn for other reasons, n (%)	9 (19.6%)	2 (8.3%)

Table 30: Demographic characteristics of Study 058 population

		TQ	CQ + PQ
Sex, n (%)	Males	37 (80.4%)	20 (83.3%)
	Females	9 (19.6%)	4 (16.7%)
Age, years	Mean (SD)	25.5 (6.37)	29.7 (8.57)
Race	Oriental	46 (100.0%)	24 (100.0%)

Table 31: Primary efficacy results (Study 058; PP population)

	TQ	CQ + PQ
Proportion of PP Subjects with Confirmed *P. vivax* Malaria, with an ACR to Treatment 28 Days after Initiation of Dosing		
N (PP)	43	22
ACR, n (%)	40 (93.0)	22 (100)
ETFs	3 (7.0)	0
Exact 90% CI for ACR	(82.9, 98.1)	(87.3, 100.0)

Table 32: Primary efficacy results (Study 058; ITT population)

	TQ	CQ + PQ
Proportion of ITT Subjects with Confirmed *P. vivax* Malaria, with an ACR to Treatment 28 Days after Initiation of Dosing		
N (ITT)	46	24
ACR, n (%)	40 (87.0)	22 (91.7)
ETFs	5 (10.9)	0
Late Treatment Failures	1 (2.2)	2 (8.3)
Exact 90% CI for ACR	(75.9, 94.2)	(76.0, 98.5)

Table 33: Secondary efficacy results (Study 058)

Endpoint	**TQ**	**CQ + PQ**
Prevention of *P. vivax* Relapse		
N (Day 90 PP)	38	20
Cleared at Day 28, n (%)	35 (100.0%)	20 (100.0%)
Relapsed by Day 90, n (%)	0	1 (5.0%)
Without relapse by Day 120, n (%)	35 (100.0%)	19 (95.0%)
90% CI (subjects without relapse by Day 120)	(91.8, 100.0)%	(78.4, 99.7)%
N (Day 90 ITT)	46	24
Cleared at Day 28, n (%)	40 (100.0%)	22 (100.0%)
Relapsed by Day 90, n (%)	0	1 (4.5%)
Without relapse by Day 120, n (%)	35 (87.5%)	19 (86.4%)
Invaluable by Day 120, n (%)	5 (12.5%)	2 (9.1%)
90% CI (subjects without relapse by Day 120)	(75.5, 94.9)%	(68.4, 96.2)%
Parasite Clearance Time (PCT)		
N (PP)	44	24
PCT Mean hours (SD)	82.5 (32.33)	40.0 (15.69)
Cleared by Day 7, n	41	24
Not cleared by Day 7, n	3	0
N (ITT)	46	24
PCT Mean hours (SD)	83.4 (31.85)	40.0 (15.69)
Cleared by Day 7, n	43	24
Not cleared by Day 7, n	3	0

6.3.1.3. Evaluator comments

A three day dosing regimen of 400 mg tafenoquine per day demonstrated gametocytocidal activity but did not achieve the primary endpoint as there were three ETFs and the study had been designed to conclude sufficient efficacy if no more than two ETFs occurred on tafenoquine. The onset of action of tafenoquine was noticeably slower than the standard treatment regimen of chloroquine plus primaquine, but resulting in longer parasite and fever clearance times. Although this was not an objective of this study, tafenoquine was highly efficacious (100%) for the prevention of Pv relapse. None of the 35 subjects receiving tafenoquine with an adequate clinical response at Day 28 and who remained evaluable during the follow-up period to Day 120 had a relapse of malaria. Among the 20 evaluable subjects receiving chloroquine plus primaquine, there was one relapse (on Day 63) during the follow-up period.

6.3.2. Study 047

Study 047 was a randomised, open label, dose ranging study evaluating the safety and efficacy of tafenoquine in preventing relapse of Pv malaria in Thailand. Specifically, the study investigated the complete elimination of hypnozoites from the liver (relapse prevention). The study further aimed to investigate the safety and PK of tafenoquine in normal and infected populations and to determine the tafenoquine concentrations associated with clinical outcomes.

Although the study was open label, the objective assessment of parasitaemia for the protective efficacy outcome was performed by slide readers who were blinded to the participants' treatment assignments. Participants with parasitological confirmation of Pv received 600 mg chloroquine immediately (Day -5) then 300 mg at 6 hours, 24 hours (Day -4), and 48 hours (Day -3), and were subsequently randomised to one of four treatment arms (tafenoquine 300mg, once daily for 7 days; tafenoquine 500 mg, once daily for 3 days followed by an additional 500 mg once daily for 3 days beginning 1 week after the first dose; tafenoquine 500 mg as a single dose; or no further treatment). Safety and tolerability data from the first 2 weeks were used to determine the treatment regimens for an additional group of participants randomised to one of five treatment arms irrespective of any remaining parasitaemia (tafenoquine 300 mg once daily for 7 days; tafenoquine 600 mg, once daily for 3 days; tafenoquine 600 mg as a single dose; no further treatment; or primaquine base 15 mg once daily for 14 days). Samples for PK analysis were collected 8 to 14 hours and 20 to 48 hours post dose throughout the dosing period and in Weeks 2, 3, 4, 6, 8, 12, 16, 20 and 24 post-dosing.

All participants with confirmed malaria were pre-treated for malarial infection with chloroquine 600 mg once and chloroquine 300 mg once daily for 3 days. Ninety-six (96) participants were assigned to the plasma tafenoquine PK population.

6.3.2.1. Results

Three participants relapsed during the study. In 2 of the 3 relapsed subjects, blood concentrations of tafenoquine were similar to those of non-relapsed subjects in the same treatment group, while the third relapsed subject had peak tafenoquine concentrations that were lower than those in non-relapsed subjects. This was not statistically significant.

6.3.3. Study 049

This study was for the evaluation of tafenoquine for the post-exposure prophylaxis of Pv malaria (Southwest Pacific Type) in non-immune Australian soldiers. It was conducted in Australia between 1 February 1999 and 30 April 2000. The objective of the study was to compare the effectiveness and tolerability of tafenoquine with primaquine in preventing Pv malaria after leaving a malarious area.

6.3.3.1. Study design

This was an open-label, randomised, parallel group study in male and female members of the ADF who had been stationed in the Southwest Pacific. Subjects had been taking daily

doxycycline as malaria prophylaxis during deployment. Three distinct cohorts were enrolled into the study: AMI 001 (Papua New Guinea), AMI 002 and AMI 003 (East Timor). Subjects who met the entry criteria (healthy, G6PD-normal, free from malaria) were randomised to receive primaquine (7.5 mg daily for 14 days) or tafenoquine:

- 400 mg OD for three days (AMI 001 and 002)
- 200 mg BID for three days (AMI 001 and 002)
- 200 mg OD for three days (AMI 003)

Randomisation was in the ratio (Primaquine: Tafenoquine) 1:1 for AMI 001, 1:2 for AMI 002, and 1:3 for AMI 003. Subjects were evaluated at Screening and Day 4 (last day on deployment), when blood samples were taken for haematology, biochemistry, and PK analysis. Subjects were followed up for 12 months for the development of relapse of Pv. If relapse occurred, this was treated with chloroquine (3 days) followed by tafenoquine (3 days).

6.3.3.2. Study population

Subjects included were consenting G6PD-normal adults, between 18 and 55 years of age, in good health. All subjects were G6PD-normal and gave written informed consent.

6.3.3.3. Treatment and administration

Subjects were randomised to receive either primaquine or tafenoquine as described above. The study drug was supplied as follows:

- Primaquine: each tablet contained 7.5 mg primaquine
- Tafenoquine: each capsule contained 250 mg (200 mg base equivalent) tafenoquine

All study volunteers randomised to primaquine were to continue doxycycline 100 mg for 2 weeks on leaving the deployment area in accordance with ADF policy at the time.

6.3.3.4. Efficacy parameters

The primary efficacy parameter was the proportion of subjects with confirmed parasitaemia during the 12 month Follow-up period. The secondary efficacy variable was time to confirmed parasitaemia during the 12 month follow-up period.

6.3.3.5. Statistical methods

The PE analysis consisted of a chi-squared test of independence (and associated 95% CI) for the number of failures in each tafenoquine group versus primaquine. A Fisher's exact test was also performed as low failure rates were observed for some of the treatment groups. Most subjects were male, and the demographics were similar between the groups.

6.3.3.6. Efficacy results

The efficacy analysis was based on the ITT population.

Primary efficacy variable

The primary efficacy parameter was the proportion of subjects with confirmed parasitaemia during the 12 months following initial eradication. Results were very similar between all the treatment groups. In the tafenoquine 400 mg or 200 mg BID groups, over 97% were parasitaemia free (similar to the primaquine group) and in the treatment group that received tafenoquine 200 mg, this number was over 95% (once again, similar to the primaquine group). These results are summarised for each cohort in Tables 34 to 36.

Table 34: Confirmed parasitaemia Cohort AMI 001 (Study 049)

Parasitemia	Treatment Group		
	Primaquine	Tafenoquine	Tafenoquine
	7.5 mg tid	200 mg bid	400 mg od
	N = 210	N = 86	N = 288
No confirmed parasitemia	205 (97.6%)	85 (98.8%)	282 (97.9%)
Confirmed parasitemia	5 (2.4%)	1 (1.2%)	6 (2.1%)
Treatment Comparison (Tafenoquine – Primaquine)			
95% CI for comparison	-	-4.3%, 1.85%	-2.9%, 2.34%
P-value (chi-square)	-	0.49955	0.82341
P-value (Fisher's exact)	-	0.67581	1

Table 35: Confirmed parasitaemia, Cohort AMI 002 (Study 049)

Parasitemia	Treatment Group		
	Primaquine	Tafenoquine	Tafenoquine
	7.5 mg tid	200 mg bid	400 mg od
	N = 131	N = 75	N = 158
No confirmed parasitemia	113 (86.3%)	71 (94.7%)	141 (89.2%)
Confirmed parasitemia	18 (13.7%)	4 (5.3%)	17 (10.8%)
Treatment Comparison (Tafenoquine – Primaquine)			
95% CI for comparison	-	-17%, -1.2%	-11%, 4.06%
P-value (chi-square)	-	0.04617	0.34993
P-value (Fisher's exact)	-	0.06406	0.37544

Table 36: Confirmed parasitaemia, Cohort AMI 003 (Study 049)

Parasitemia	Treatment Group	
	Primaquine	Tafenoquine
	7.5 mg tid	200 mg od
	N = 158	N = 406
No confirmed parasitemia	151 (95.6%)	386 (95.1%)
Confirmed parasitemia	7 (4.4%)	20 (4.9%)
Treatment Comparison (Tafenoquine – Primaquine)		
95% CI for comparison	-	-3.3%, 4.33%
P-value (chi-square)	-	0.80442
P-value (Fisher's exact)	-	1

Secondary efficacy variable

The secondary efficacy variable was time to parasitaemia. In Cohorts AMI 001 and AMI 003, the Kaplan-Meier survival curves for all treatments were almost superimposed on each other. For Cohort AMI 002; however, there was some separation of the curves showing longer times to parasitaemia in the tafenoquine 200 mg BID and tafenoquine 400 mg daily groups, than in the primaquine 7.5 mg three times daily group.

6.3.3.7. Conclusion

This study found that a three day dosing regimen of tafenoquine (400 mg OD, 200 mg BID or 200 mg OD) were all similarly effective as a post-exposure prophylaxis agent in this study, demonstrating similar efficacy to 14 day primaquine. This is standard practice in returning ADF

personnel. The incidence of malaria in these personnel untreated is not available (no placebo group). Tafenoquine, with a short dosing regimen (three days compared to 14 days primaquine), could be used as effective, post-exposure prophylaxis agent.

6.3.4. Challenge Studies 053 and 054

These two studies were conducted for the evaluation of tafenoquine as a prophylactic agent against induced Pf malaria infection in healthy non-immune subjects: a dose ranging study and a multiple dose causal versus suppressive study. The prophylactic efficacy of single dose (Study 053) and multiple dose (Study 054) tafenoquine was assessed with a human Pf challenge model. Both studies used a randomised, double blind, placebo controlled design in active duty, non-immune, healthy male and female US military volunteers. All participants were exposed to mosquitoes infected with a chloroquine sensitive clone (NF54) of Pf. Participants who developed parasitaemia were treated with the standard oral regimen of 600 mg (base) of chloroquine followed by 300 mg of chloroquine at 6, 24 and 48 hours. Study 053 was intended to be conducted in three sequential phases: tafenoquine 600 mg or placebo administered one day prior to sporozoite inoculation (Group 1); tafenoquine 600 mg or placebo administered one week prior to sporozoite inoculation (Group 2); or tafenoquine 400 mg or placebo administered one week prior to sporozoite inoculation (Group 3). In Group 1, when either tafenoquine 600 mg (n=4) or placebo (n=2) was given one day prior to sporozoite inoculation, three of the 4 subjects who received tafenoquine were protected from malaria, while the fourth subject developed parasitaemia. Because a single dose of tafenoquine 600 mg administered one day prior to inoculation was not effective in preventing symptomatic malaria in all four subjects of Group 1, the study was discontinued after the first group of participants was treated.

In Study 054, 10 participants received two 600 mg doses of tafenoquine (Day -3 and -2) in the fed state prior to sporozoite inoculation (Day 0) and half of the participants were then randomised to tafenoquine 300 mg on Days 3, 10, 17 and 24 or tafenoquine 600 mg on Day 3 and placebo on Days 10, 17, and 24. Two participants received placebo only (both before and after inoculation). Six out of the 10 drug treated individuals developed asymptomatic parasitemia. This would suggest that, if tafenoquine has causal prophylactic activity, the dosing regimen used may not kill all of the tissue stage parasites of this strain. Five of these six individuals were treated with chloroquine; the remaining sixth volunteer was not treated, but observed, and his parasitaemia spontaneously cleared. Recent in vitro blood schizonticidal sensitivity studies suggested that the NF54 parasite is several times less susceptible to tafenoquine than most other isolates, including new multi-drug resistant isolates from South East Asia. However, the prolonged half-life may result in persistently high enough concentrations such that this drug can act as a suppressive prophylactic.

Study 053 and Study 054 both determined the PK profile of tafenoquine. In Study 053, the single subject who developed parasitaemia had a peak plasma tafenoquine concentration of 182 ng/mL as compared with 417 to 489 ng/mL peak levels in the protected participants. In contrast, $t_{½}$ was comparable between relapsed and healthy individuals (in range of 329 to 441 hours). In Study 054, C_{max} (mean), T_{max} (median) and $t_{½}$ (median) were 358 ng/mL, 11.9 hours, and 19.5 days (468 hours), respectively with coefficients of variation of 24%, 41%, and 23%, respectively. Clearance and apparent volume of distribution were not calculated from Study 053 and Study 054 data.

6.3.5. Study 006

This study was a dose down range placebo controlled double blind study of oral tafenoquine for prophylactic efficacy, safety, and tolerance in subjects resident in a malarious area of Gabon. Study 006 was a double blind, randomised Phase II clinical trial conducted to evaluate the prophylactic efficacy, safety and tolerance in participants resident in an endemic malarial area of Gabon. Participants (N = 415) were randomly assigned to a treatment group (tafenoquine 25,

50, 100 or 200 mg once daily for 3 days, 80 to 86 participants per dose; or placebo once daily for 3 days, 83 participants). Samples were collected for PK analysis 7 and 14 days after first dose.

The primary efficacy variables were time to malaria parasitaemia in thick blood smear, and PE of tafenoquine at 49 days. The secondary efficacy variables were PE of tafenoquine at 42 and 70 days, and clinical response (successful or unsuccessful) according to the Investigator's clinical opinion. This was termed 'clinical outcome' in the protocol.

The principal reason for withdrawal was protocol violation (including non-compliance). Withdrawal due to loss of prophylactic efficacy was highest in the placebo and tafenoquine 25 mg groups (both approximately 14%) and there were no marked differences between the groups in the proportions of subjects withdrawn due to AEs. Subjects were aged between 12-20 years of age and all were Black African. Males (47.5%) and females (52.5%) were approximately evenly distributed between treatments. Disposition of subjects is shown in Table 37.

Table 37: Disposition of PK treatment population (Study 006)

Population	Treatment Group					Total
	TQ 25 mg	TQ 50 mg	TQ 100 mg	TQ 200 mg	Placebo	
Screened						426
Randomized	80	86	82	84	83	415
Intention-to-treat population	80	86	82	84	83	415
Completed study	61	73	61	74	58	327
Per protocol population	44	64	52	61	52	273
Safety population	80	86	82	84	83	415

6.3.5.1. Efficacy results

The PE of tafenoquine at Day 49 is summarised in Table 38 for the ITT population. PE at Day 49 was chosen as the primary efficacy variable since it would determine whether a short course of tafenoquine could potentially provide protection from malaria infection during a 4 week trip, taking into account the two-three week latency between an infected mosquito bite and time to development of parasitaemia.

Table 38: Protective efficacy of tafenoquine, Day 49 (Study 006)

Protective Efficacy at Day 49	Treatment Group			
	TQ 25 mg	TQ 50 mg	TQ 100 mg	TQ 200 mg
	N = 80	N = 86	N = 82	N = 84
Known Dataset				
Protective efficacy	17.9%	100%	100%	100%
95% CI	(-173%, 75.4%)	(29.6%, 100%)	(22.4%, 100%)	(27.9%, 100%)
Worst Case Dataset				
Protective efficacy	19.3%	78.6%	32.5%	78%
95% CI	(-99.5%, 67.6%)	(15.3%, 94.7%)	(-74%, 74.0%)	(13.4%, 94.6%)

The lowest dose of tafenoquine tested in the study (25 mg) offered little protection over placebo; whereas, the three higher doses provided 100% PE over placebo. The associated 95% CI for these comparisons had very low lower limits, due to there being only a small proportion of failures in the placebo group, which, with the sample sizes employed in the study, leads to an imprecise estimate of PE. In the worst case dataset, the rates of PE were considerably reduced

because missing outcomes were counted as failures and PE is highly sensitive to changes in the failure rate.

Secondary efficacy variables

The PE of tafenoquine at Day 42 and Day 70 is summarised in Table 39 for the intent-to-treat population known datasets. These additional time points were examined to see if tafenoquine provided a shorter or longer period of protection than expected from data of previous studies.

Table 39: Protective efficacy of tafenoquine (secondary outcomes), Days 42 and 70 (Study 006)

Protective Efficacy	Treatment Group			
	TQ 25 mg	TQ 50 mg	TQ 100 mg	TQ 200 mg
	N = 80	N = 86	N = 82	N = 84
Day 42, Known Dataset				
Protective efficacy	24%	100%	100%	100%
95% CI	(-195%, 80.5%)	(11.8%, 100%)	(2.7%, 100%)	(9.7%, 100%)
Day 70, Worst Case Dataset				
Protective efficacy	-15%	72%	91.7%	100%
95% CI	(-117%, 38.2%)	(16.4%, 91.1%)	(53.7%, 98.6%)	(70.5%, 100%)

At Day 42 results were similar to those at Day 49. At Day 70, the PE suggest an increasing level of protection as the dose increases, with the tafenoquine 25 mg group showing no benefit over placebo. The cumulative totals of the number of subjects with an unsuccessful clinical response (clinical outcome) as rated by the Investigator at the Day 42, Day 49, and Day 70 visits are shown in Table 40.

Table 40: Summary of subjects with unsuccessful clinical response (Study 006)

Visit	Treatment Group				
	TQ 25 mg	TQ 50 mg	TQ 100 mg	TQ 200 mg	Placebo
	N = 80	N = 86	N = 82	N = 84	N = 83
Day 42	3	0	0	0	3
Day 49	4	0	0	0	4
Day 70	15	2	2	0	14

Study 006 included a population of 216 adolescents (ages 12 to 17) who received tafenoquine loading doses of 25, 50, 100, or 200 mg daily x 3 days. Overall, the adolescents showed good efficacy results for doses above 25 mg/day, with 100% prophylactic success at the 200 mg dose and only slightly lower efficacy for 100 mg (96.2%) and 50 mg (98.0%).

6.3.6. Study 030

This was a randomised, double blind, placebo controlled evaluation of weekly tafenoquine compared to mefloquine for chemo-suppression of Pf in Western Kenya, to evaluate the chemoprophylactic efficacy of weekly tafenoquine in preventing Pf parasitaemia post-initial parasite clearance. The study further aimed to assess the safety, tolerability and population PK of tafenoquine compared with placebo and mefloquine.

Healthy volunteers of either sex aged between 18 and 55 years planning to reside in the study area for the entire study period of approximately 70 weeks were eligible for entry into the study.

Participants (N = 36) were treated for 3 days with halofantrine to clear any existing parasitaemia then randomised into one of three treatment arms (tafenoquine 200 mg once daily for 3 days, followed by tafenoquine 200 mg once weekly for 24 weeks; mefloquine 250 mg once daily for 3 days, followed by mefloquine 250 mg once weekly for 24 weeks; or placebo). Samples for PK analysis were collected on Day 2 (6 to 12 hours after third loading dose) and at Weeks 4, 8, 16, 17 and 28. All tafenoquine plasma concentrations were > 100 ng/mL following the loading doses and weekly dosing up to 4 weeks after the first loading dose. Plasma concentrations observed in subjects who failed on treatment and those who did not fail were similar during both loading dosing and during prophylactic treatment.

6.3.6.1. Efficacy parameters

The primary efficacy variable was prophylactic outcome (success/failure) at the end of the prophylactic treatment phase (time of last dose, Week 24, plus 7 days); prophylactic outcome was based on absence/presence of asexual stage parasites of any Plasmodium species on a single blood smear. The secondary efficacy variables were: number of subjects with two consecutive positive smears during prophylactic treatment; number of subjects with a first positive smear (Pf species only) during prophylactic treatment; time to first positive smear; time to two consecutive positive smears. (Secondary efficacy analyses from results during the safety Follow-up period were not performed due to the high early withdrawal rate from the study due to false-positive malaria microscopy).

6.3.6.2. Statistical methods

The primary efficacy analysis was based on a calculation of the PE of tafenoquine, defined as (1; relative risk of developing parasitaemia with tafenoquine: placebo) x 100%, and 95.2% CI were constructed for the relative risk using Koopmans' method.

The PEs of tafenoquine and mefloquine based on the secondary endpoints were also calculated, together with 95% CI. Kaplan-Meier survival curves were produced for time to parasitaemia for both first positive smear and two consecutive positive smears.

6.3.6.3. Withdrawals due to adverse experiences

Thirteen subjects had AEs recorded as leading to withdrawal: 10 (3.3%) during the prophylaxis treatment phase and five (1.6%) during Follow-up (two subjects had events during both phases). Most of these withdrawals were due to apparent parasitaemia, with the reason for withdrawal from the study being given as 'insufficient therapeutic effect'.

6.3.6.4. Efficacy results

High failure rate

Early in the study, it became apparent that the failure rate was higher than would be expected for the design including two effective chemoprophylactic treatment arms. The failure rate leads to a series of investigations into the possible cause, and the setting-up of an Independent Data Monitoring Committee (IDMC), to assess whether it was appropriate to continue the study. A re-read of a sample of study slides by two separate, experienced, slide-reading centres, the Naval Medical Research Unit-2 (NAMRU-2), Jakarta, and the Australian Army Malaria Institute, Brisbane, suggested high rates of false positives were being identified at the study site. In parallel, and in concert with this conclusion, the IDMC conducted an unblinding of parasitaemia results from the centre and identified low apparent PE for both tafenoquine and mefloquine groups. The IDMC concluded that the study should continue in order to meet the secondary objectives of evaluating the long-term safety and efficacy of tafenoquine.

It is assumed that the re-reading done by NAMRU-2 were correct, for all re-read slides the sensitivity (the proportion of true positives correctly identified by USAMRU-K) was 86.1% (31/36) and the specificity (the proportion of true negatives correctly identified) was 69.8% (507/726). The overall concordance rate was 70.6% (538/762), with the negative concordance

rate being 99% (507/512) and the positive concordance rate being only 12.4% (31/250). This correlation is shown in Table 41. With such a low positive concordance results, the efficacy results and analyses from this study cannot be considered meaningful.

Table 41: Correlation of second reading of blood slides in Study 030

USAMRU-K Reading	NAMRU-2 Reading		
	Positive	Negative	Total
Positive	31	219	250
Negative	5	507	512
Total	36	726	762

6.3.6.5. Primary efficacy variable

Prophylactic outcome and PE based on first positive smear (all species), original reading. As expected following the slide-reading errors, PEs for both tafenoquine and mefloquine relative to placebo are low (Table 42).

Table 42: Prophylactic outcome, Study 030 ITT population (these results are probably inaccurate)

Prophylactic Outcome	Treatment Group		
	Placebo N = 99	Tafenoquine 200 mg N = 102	Mefloquine 250 mg N = 99
Prophylactic failure	93 (93.9%)	90 (88.2%)	92 (92.9%)
Prophylactic success (total)[a]	6 (6.1%)	12 (11.8%)	7 (7.1%)
Prophylactic success (known)[b]	0	6 (5.9%)	0
Prophylactic success (assumed)[c]	6 (6.1%)	6 (5.9%)	7 (7.1%)
PE[d] (%)	-	6.1%	1.1%
95.2% CI	-	-2.8%, 15.0%	-7.4%, 9.1%

a Total success is defined as [known successes + assumed successes]. b Known success is defined as when the subject had negative smears up to and including Week 24. c Assumed success is defined as subject had negative smears throughout the study but withdrew prior to Week 24 d Protective efficacy relative to placebo based on failure rate. CI: confidence interval; N: number; PE: protective efficacy.

6.3.6.6. Secondary efficacy variables

PE based on two consecutive positive smears (all species). Protective efficacies are higher using this endpoint but cannot be regarded as a valid result due to slide-reading errors. The results for protective efficacy of tafenoquine based on Pf only were similar to those for any species. The time to first positive smear and two consecutive positive smears is summarised below for the ITT population.

Although there was a statistically significant difference between the survival curves for the tafenoquine and placebo groups for the time to first positive smear and the time to two consecutive positive smears ($p < 0.01$), the results may not be valid as almost all subjects had at least one positive smear during the study.

6.3.6.7. Conclusions

A failure of the slide-reading process in this study led to uncertainty in assessment of the primary objective that is, determining the chemoprophylactic efficacy of tafenoquine against Pf infection.

6.3.7. Study 044

Study 044 was a randomised, double blind, placebo controlled study to evaluate the efficacy, tolerability, safety and PK of tafenoquine for Pf and Pf prophylaxis in Thai soldiers. Tafenoquine (400 mg base daily for 3 days followed by 400 mg base monthly for 5 consecutive months) was compared to placebo. All participants were male soldiers in the Royal Thai Armed Forces. All participants were presumptively treated for malarial infection with artesunate for 3 days plus doxycycline for 7 days prior to study start. One hundred and four (104) participants were assigned to the tafenoquine 400 mg monthly prophylaxis group (loading plus monthly administration). Thirty-one participants were administered placebo during the study, all of whom contracted malaria. The 31 placebo participants were re-treated with artesunate and doxycycline and given a loading dose of tafenoquine, 400 mg daily for 3 days, followed by tafenoquine 400 mg weekly for prophylaxis.

6.3.7.1. Results

Efficacy (ITT) population were subjects who received at least one dose of double blind study medication and had at least one on-therapy assessment of parasitaemia (blood smear).

Primary efficacy variable

Tafenoquine was highly efficacious in preventing Pf and Pv malaria during the double blind treatment phase. There was one treatment failure on tafenoquine compared with 30 treatment failures on placebo. The failure on tafenoquine occurred 35 days after the most recent monthly dose (second monthly dose) due to the subject missing their scheduled monthly dosing day; at this point PK analysis showed that the serum levels were particularly low in this individual. The PE based on cumulative malaria attack rate relative to placebo is shown in Table 43.

Table 43: Protective efficacy of tafenoquine relative to placebo in Study 044

	Treatment Group	
	Tafenoquine	Placebo
	N = 104	N = 101
Total Cases (Crude Attack Rate)		
All species	1 (1.0%)	30 (29.7%)
P. falciparum	0	8 (7.9%)
P. vivax	1 (1.0%)	21 (20.8%)
Mixed infection*	0	1 (1.0)
Protective Efficacy (95% CI)		
All species	**96.7% (82.0, 99.4)**	
P. falciparum	100% (54.5, 100)	
P. vivax	95.3% (73.9, 99.2)	

*Mixed parasitemia counted as both Pf and Pv in calculations of cumulative malaria attack rate and protective efficacy. CI: confidence interval; N: number.

Calculating PE based on cumulative malaria incidence density had a minimal effect on these values, either for all or individual species. Similarly, excluding three possible cases of relapsing Pv malaria from the placebo group resulted in little effect on calculated PEs of 96% (81%, 99%) against both species together, 100% (56%, 100%) for Pf and 95% (70%, 90%) for Pv alone. No study subjects going on to receive weekly 400 mg tafenoquine went on to experience a failure of prophylaxis.

6.3.8. Study TAF112582

Study TAF112582 was a double blind, randomised, parallel group, active controlled Phase II clinical study conducted to evaluate the efficacy, safety and tolerability of tafenoquine in participants with Pv malaria. Specifically, the study investigated the radical cure efficacy of Pv

malaria. Weight, sex and race were investigated as potential covariates of CL/F and central volume of distribution (V2/F). The study was conducted in seven centres across Brazil, Peru, Thailand and India. All participants were pre-treated with single 600 mg chloroquine doses on Days 1 and 2, followed by a single dose of 300 mg chloroquine on Day 3. A total of 329 participants were randomly assigned to a treatment group for coincident tafenoquine dosing in parallel. These were:

- 55 participants ; 50 mg tafenoquine single dose Day 1 or 2,
- 55 participants; 100 mg tafenoquine single dose Day 1 or 2,
- 57 participants; 300 mg tafenoquine single dose Day 1 or 2,
- 57 participants; 600 mg tafenoquine single dose Day 1 or 2, 56 participants),
- 50 participant; primaquine dosing (15 mg primaquine once daily Days 2 to 15,
- 54 participants no additional treatment.

Between 25% and 50% of participants in each treatment group were female. Samples for PK analysis were obtained during two sampling windows 4 to 8 hours and 24 to 48 hours after tafenoquine dosing and on Days 8, 29 and 60. C_{max}, T_{max} and $t_{½}$ were not reported.

6.3.8.1. Results

Fifty two (52) of 164 participants had recurrence of parasitaemia within 6 months after initial clearance. A logistic regression analysis correlated AUC with relapse status, such that probability of being relapse free at 6 months increased by 51% for each 25 unit increase in AUC above 54.5 µg h/mL.

A final time-to-event model was used to simulate the survival probability for subjects receiving a single 200 mg dose of tafenoquine (a dose level not administered in Study TAF112582). The predicted probability of being relapse free at 6 months for a single 200 mg dose was 70% (95% CI: 60% to 81%) which is slightly less than the relapse free efficacy at 6 months observed for primaquine 15 mg once daily for 14 days (77.3%) in the current study.

6.3.9. Evaluator commentary on other efficacy studies

None of the evaluable supportive studies match the dose/frequency exactly of the requested dose and indication for chemoprophylaxis. In Study 058, this was a treatment study which did not meet its primary outcome in terms of comparing tafenoquine to chloroquine for Pv treatment. It was slower in terms of fever resolution and parasite clearance. But prevention of relapse was good in the tafenoquine group (out to 4 months), after a loading dose alone. Supportive efficacy data is provided from Studies 049 (post-exposure prophylaxis in returned soldiers from Timor given a 3 day loading dose only) and 047 (relapse prevention in Thailand, using different doses of tafenoquine), which also showed equivalence of tafenoquine to standard regimens and 044 (prophylaxis in Thai soldiers) which used only a loading dose. Study TAF112582 also used only a loading dose for relapse prevention in endemic countries after treatment of Pv (and not the recommended dose). Early challenge (PD) Studies 053 and 054 have already been discussed and the challenge Study TQ-2016-02. The challenge Study TQ-2016-02 is a very good tight study which showed excellent efficacy of tafenoquine versus placebo, but it is impossible to extrapolate this data precisely to the real world environment. Study 006 was not well powered to show protection greater than placebo and used only loading doses. Study 030 has uninterpretable efficacy results because of the high rate of false positives in initial testing and should be ignored.

6.4. Analyses performed across trials: pooled and meta analyses

6.4.1. Results relevant to prophylaxis

Efficacy data based on attack rates for all studies using full prophylactic regimens of tafenoquine (loading dose followed by weekly/monthly dosing) are summarised in Table 44.

Table 44: Comparison of efficacy results across studies

Study	Analysis set	Treatment	N	No. of prophylactic failures	% Fail (95% CI)	%PE (95% CI)
043 (i)	ITT	Placebo	59	54	92 (82–96)	–
		Tafenoquine 200 mg	53	7	13 (7–25)	86 (73–93)
044	ITT	Placebo	101	30(ii)	30 (22–39)	–
		Tafenoquine 400 mg Monthly	104	1(ii)	1 (0–5)	97 (82 –99)
045	ITT	Placebo	94	86	92 (84–96)	–
		Tafenoquine 25 mg	93	58	62 (52–72)	32 (20–43)
		Tafenoquine 50 mg	91	13	14 (9–23)	84 (75–91)
		Tafenoquine 100 mg	94	11	12 (7–20)	87 (78–93)
		Tafenoquine 200 mg	91	12	13 (8–22)	86 (76–92)
		Mefloquine 250 mg	46	6	13 (6–26)	86 (72–93)
030	mITT	Placebo	93	32	34 (26–45)	–

Study	Analysis set	Treatment	N	No. of prophylactic failures	% Fail (95% CI)	%PE (95% CI)
		Tafenoquine 200 mg	99	2	2 (1–7)	94 (89 – 97)
		Mefloquine 250 mg	96	2	2 (1–7)	94 (89–99)
033	PP	tafenoquine 200 mg	462	0	0 (0–1)	–
		Mefloquine 250 mg	153	0	0 (0–2)	–
043 045 030	(As Above)	Placebo	246	172	70 (64–75)	–
	(As Above)	Tafenoquine 200 mg	243	19	8 (5–12)	89 (85 – 93)
044 033	(As Above)	Tafenoquine 200 mg /400 mg	566	1	<1	–

In Phase III trials (Studies 045 and 033) against the positive comparator mefloquine, point estimates of efficacy of tafenoquine versus comparator were essentially the same within each study. In Study 045 for Pf in African semi-immunes, PE compared to placebo was 86% for tafenoquine and 86% for mefloquine. Tafenoquine was statistically non-inferior to mefloquine. In Study 033 primarily for Pv but also with some calculated incidence of Pf in Australian non-immunes, the full prophylactic regimen of tafenoquine had efficacy identical to that of the standard mefloquine comparator: no subject had parasitaemia in either group over 6 months of prophylaxis. Historic control data indicate that 7.9% of subjects would have become infected (6.9% with Pv, 1.0% with Pf) under those conditions. Tafenoquine was statistically non-inferior to mefloquine of subjects would have become infected (6.9% with Pv, 1.0% with Pf) under those conditions.

Male versus female results from clinical studies are shown in Table 45.

Table 45: Efficacy of tafenoquine of males versus females in primary analytic populations

Baseline Characteristic *	Prophylactic African Studies 006 / 043 / 045 / 030	Prophylactic SE Asia / Oceania Studies 044 / 033	All Field Prophylactic Studies Using Loading Plus Weekly Dosing 043 / 044 / 045 / 030 / 033	*Pv* Hypnozoite and Blood Stage Treatment Studies 047 / 049 / 058	All Field Efficacy Studies 006 / 043 / 030 / 044 / 033 / 047 / 049 / 058
Efficacy in Males					
Number of	564	571	983	1043	2178
Failure, N (%)	103 (18.3)	1 (0.2)	95 (9.7)	53 (5.1)	157 (7.2)
Efficacy in Females					
Number of	414	14	248	104	532
Failure, N (%)	41 (9.9)	0(0)	31 (12.5)	1 (1.0)	42 (7.9)

*The primary analytic populations for each study were: 006 – ITT known data set population; 043 – ITT population; 044 – ITT population; 045 – ITT population; 030 – mITT population; 033 – PP population; 047 – ITT population; 049 – ITT population; 058 – PP population.

Few subjects of high weight were included in the clinical studies in this dossier. In Study 045, mean weight in each dosing group between tafenoquine 50 mg and tafenoquine 200 mg was 54 kg to 57 kg (males) and 45 kg to 50 kg (females). These narrow weight ranges mean that subjects in the 50 mg dose group received approximately 1 mg/kg each dose for both males and females and subjects in the 200 mg dose group received approximately 4 mg/kg each dose for both males and females. In spite of the difference in dosing on a weight basis, PE was almost the same: 84% in the 50 mg dose group and 86% in the 200 mg dose group. The comparative efficacy between subjects receiving 1 mg/kg each dose and 4 mg/kg each dose in Study 045 suggests that even subjects weighing 100 kg, who would receive 2 mg/kg each dose with the proposed prophylactic regimen of 200 mg each dose, would not be more likely to fail than a 65 kg person who would receive 3 mg/kg each dose. In the final model based on clinical data from Studies 001, 002, 003, 004, 005, 014, 015, 033, 044, and 058, tafenoquine 200 mg once daily for 3 days followed by tafenoquine 200 mg weekly generated plasma tafenoquine concentrations > 80 ng/mL immediately after the loading dose in 95% of individuals and in all individuals post-first trough. The simulated tafenoquine concentration was sustained above 80 ng/mL irrespective of weight (or meal schedule or age).

6.4.2. Summary of post-exposure studies

Data from Studies 033, 047, 049, and 058 shows that the tafenoquine anticipated clinical regimen is as effective as the standard course of primaquine in preventing Pv relapse. Data also comes from the DETECTIVE study publication (Study TAF112582) in which several tafenoquine dosing regimens were compared to primaquine.[6] The ability to eliminate asexual blood stages is one of the four types of studies suggested by the FDA malaria guidance[4] to support the prophylactic indication.

6.5. Evaluator's conclusions on clinical efficacy

There are a variety of clinical efficacy studies, Study 033 was originally submitted as the pivotal study for the indication requested. Study 045 was added to provide additional supporting data in semi-immunes. The other studies are supportive and include both immune and non-immune individuals. The data from the other studies is discussed above and although there is good evidence of efficacy of tafenoquine similar to weekly standard of care for prophylaxis (except Study 030), the supportive studies all used different dosage regimens and so cannot be used to exactly support the proposed regimen. Even the most recent challenge study, although it shows very good efficacy, it is in a laboratory setting not a field environment. Study 033 is the only study that specifically reflects the main situation for use of this drug in Australia (non-immunes going to endemic countries). Only Study 033 reflects the relevant population and usage being requested and the size of this study is quite small and homogenous, not necessarily reflective of Australian non-immunes travelling to endemic areas. Study 049 also shows efficacy post-exposure prophylaxis (after return from an endemic area).

Study 045 shows efficacy in a semi-immune group (in whom it is used after malaria eradication therapy). And Study 043 also shows efficacy in semi-immunes when used for prophylaxis, although this is a dose ranging study and the numbers of participants treated with the same dose as currently being recommended is small. Study TQ-2016-02 is a powerful study in terms of showing the prophylactic efficacy of tafenoquine against Pf, but in a very controlled exposure setting. Study 058 was unable to show it primary efficacy outcome; tafenoquine was inferior in primary treatment of Pv but did show good prophylactic efficacy (a secondary outcome).

Although Pf and Pv are the most commonly acquired forms of malaria from South East Asia, in the field studies, it is impossible to comment as to the efficacy of tafenoquine against the different forms seen globally.

Other issues include the unreliability of the efficacy data from Study 030 because of overcalling of positive smears and only a low correlation with expert review of blood smears for malaria diagnosis with a specificity of less than 70%.

7. Clinical safety

7.1. Studies providing evaluable safety data

Tafenoquine has undergone clinical evaluation under a variety of development programs, including malaria chemoprophylaxis, post-exposure prophylaxis, malaria treatment, and malaria relapse prevention. All of the efficacy studies and a number of the PK studies (Studies 050 and 051) also collected tolerability and safety data. The safety Studies 001 and 057 are outlined below.

7.1.1. Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

7.1.2. Pivotal and/or main efficacy studies

There are a variety of different dosing regimens used and the efficacy study safety data has been pooled into a shorter term use, the anticipated clinical regimen (ACR) and also an 'extended dosing safety set' as shown in Table 46. The extended dosing safety set was comprised of the majority of malaria prophylaxis studies (Studies 030, 033, 043, 044 (placebo group only) and 045 plus the Phase I renal-ocular safety study (Study 057). Studies 030, 033, 043, 045, and 057 employed the tafenoquine ACR. The numbers of subjects in the tafenoquine ACR were 825, the number of placebo subjects was 396, and the number of subjects taking active comparator mefloquine in those studies was 309. The weekly dosage duration ranged from 10 to 26 weeks.

Safety evaluations focused on parameters that previous clinical experience with primaquine or non-clinical data with tafenoquine suggested might be seen clinically: nausea, abdominal pain, diarrhoea, gastroesophageal reflux disease (GORD), flatulence, headache, dizziness, dysgeusia, and insomnia. In addition, new types of AEs that were documented at higher doses than the ACR included anaemia, thrombocytopaenia, haemolysis, increased methaemoglobinaemia, and keratopathy. Table 46 outlines the contributions of each of the studies to safety analysis sets.

Table 46: Pooled analysis groups of clinical trials; safety analysis of tafenoquine

Pooled Analysis Group	Population of Analysis Group	Studies Contributing
Short Term Exposure Data Set	Subjects receiving daily tafenoquine for a period of only 1-3 days. Group includes the majority of Phase I studies and 4 Phase II studies. Study doses ranged from 2 mg (single dose) to 500 mg daily x 3 days.	003, 006, 014, 022, 040, 043, 047, 049, 050, 052, 053, 058
[a]Clinical Use Studies	Phase II-III prophylaxis and treatment studies (006, 030, 033, 043, 044, 045, and 049) plus Phase I Study 057 (the Renal-ocular Safety Study) which utilised the ACR of Tafenoquine.	006, 030, 033, 043, 044, 045, 049, 057 and 058
[b] Extended Dosing Safety Set	Subjects receiving a 3 day loading dose of tafenoquine followed by weekly or monthly exposure in controlled trials. All studies that utilised extended (weekly or monthly) dosing regimens of tafenoquine were included in this group, including the anticipated clinical regimen (ACR). Group consists of the majority of Malaria Prophylaxis Studies (Studies 030, 033, 043, 044, and 045) and the Phase I Renal-ocular Safety Study (Study 057).	030, 033, 043, 044, 045, 057

[a] Included studies relevant to tafenoquine dose response. [b] Included all comparator controlled studies that utilised the tafenoquine anticipated clinical regimen (ACR) of 200 mg daily for 3 days followed by once weekly dosing of 100 mg for up to 26 weeks.

7.2. Studies with safety as the sole primary outcome

7.2.1. Study TAF110027

This was a Phase I study to investigate the haemolytic potential of tafenoquine in healthy female subjects with G6PDD and the safety and tolerability of tafenoquine in acute Pv malaria patients with G6PDD. Conducted between July 2009 and April 2013 at two centres in Thailand.

7.2.1.1. Study design

This was an open label, single dose, dose-escalation study using a stepwise risk exposure approach. The haemolytic potential of tafenoquine (TQ) was assessed and the dose-response relationship investigated in G6PD heterozygous (WHO Class Ill variant) female healthy volunteers (without the influence of disease related confounding factors). G6PD-normal female healthy volunteers were enrolled as the control with both groups receiving TQ (that is, no placebo was used). The HND was defined as the highest dose of TQ at which no more than two out of six subjects experienced a dose limiting toxicity (DLT; defined as a ≥2.5 g/dL decline in Hb (or Hct decline of 7.5%) from baseline or any clinically significant signs and symptoms. For the dose escalation phase, G6PD heterozygous female healthy volunteers with enzyme activity range 40 to 60% of the site median normal value were recruited. Once the HND had been defined, additional cohorts exploring the haemolytic potential of TQ in G6PDD heterozygous females with 61 to 80% and 81%+ enzyme activity of the site median normal value were recruited in parallel. The mean of the Hb/Hct values obtained on Day -1 and Day 1 (prior to TQ dosing) was considered the baseline value. If more than two out of six G6PDD subjects experience a DLT at a given dose level, dose escalation was stopped. The TQ dose could have been adjusted either up or down (that is, intermediate dose levels could be assessed) until the HND had been determined (maximum dose 600 mg). This phase of the study also assessed the haemolytic potential of primaquine 15 mg OD x14 days, when given to G6PD-normal and G6PDD (with 40 to 60% enzyme activity) heterozygous females as a control arm. Following screening, subjects were treated on Day 1 (Day 1 to Day 14 for primaquine cohort) with daily assessments up to and including Day 14, and follow-up assessments on Day 21, Day 28 and Day 56.

7.2.1.2. Treatment

For the dose escalation phase, proposed total TQ doses of 100 mg, 200 mg, 300 mg, 400 mg, and 600 mg (doses less than 100 mg or intermediate dose levels could have been assessed) were planned, to be administered as a single dose. Once the HND had been defined, subsequent cohorts comprised a single dose of TQ (HND) and primaquine 15 mg x 14 days were included in the PK

7.2.1.3. Study population

Females between 18 and 45 years of age, inclusive, who were non-pregnant, non-lactating and of non-child bearing potential were eligible for inclusion. All subjects were required to have WHO class III G6PDD or G6PD-normal status prior to TQ dosing. G6PDD subjects (WHO class Ill variant) were required to be heterozygous with 40% to 60% enzyme activity of the site median normal value (minimum 2.2 IU/g Hb) in the dose escalation and primaquine cohorts. G6PD-normal subjects must have had >80% enzyme activity of the site median normal value in the dose escalation and primaquine cohorts. Once the HND was defined, G6PDD subjects (WHO class III variant) were required to be heterozygous with either 61% to 80% or 81%+ enzyme activity of the site median normal value in the subsequent TQ cohorts.

7.2.1.4. Conclusion

This Phase I dose escalation study successfully recruited three cohorts of controls and Class Ill heterozygous deficient healthy volunteer females (40 to 60% enzymatic activity) and has identified 300 mg as the highest tolerated TQ dose in this population. Despite Hb declines of up

to 30 g/L (nadirs between Day 6 and Day 14), no specific AEs relating to anaemia were reported in the TQ 300 mg cohort. In addition, in subjects with the same level of G6PD activity daily dosing of primaquine (15 mg) demonstrated similar levels of Hb decline, with only one subject completing the full 14 day dosing course. In the 13 heterozygous G6PDD females who were dosed with TQ 200 mg, there appeared to be a weak association between enzyme activity and Hb decline.

7.2.2. Study 057

This was a randomised, double blind, placebo controlled study to evaluate the safety and tolerability, specifically renal and ophthalmic effects, of tafenoquine 200 mg for 6 months, in healthy volunteers. This Phase I study assessed renal and ophthalmic safety of tafenoquine versus placebo, administered for a period of 24 weeks to healthy volunteers. The results of the primary renal analysis, which assessed the mean change from Baseline in glomerular filtration rate (GFR), demonstrated non-inferiority of tafenoquine relative to placebo, and these results were supported by both sensitivity analyses. The results of the primary ophthalmic analysis, which assessed night vision via the forward light scatter test (FLST) showed un-impairment of night vision in the tafenoquine group and this finding was supported by one of the two sensitivity analyses. No subject in the study had abnormal laboratory values indicative of potential haemolysis. Tafenoquine was well tolerated by the subjects in this study, as evidenced by the low rate of withdrawal from treatment/study due to AEs. The adjusted mean GFR increased from Baseline to Week 24 in both treatment groups. The results of this analysis demonstrate that tafenoquine is non-inferior to placebo, since the lower boundary of the CI for the treatment difference (-0.168 mL/s/1.73 m^2) is greater than the non-inferiority margin of -0.247 mL/s/1.73 m^2. The results of the primary ophthalmic safety analysis using the modified observed case dataset clearly show that night vision, as assessed via the FLST, was un-impaired in the tafenoquine treated group, since the lower bound of the one-sided 95% Clopper-Pearson Exact CI was greater than 90%.

7.3. Patient exposure

The safety database included in this dossier for tafenoquine includes data from 3184 subjects who were exposed to tafenoquine, of whom 825 (most of which were healthy volunteers) were administered the ACR of 200 mg daily for 3 consecutive days, followed by 200 mg once weekly for up to 6 months. Supportive information regarding the safety of tafenoquine is primarily drawn from healthy volunteers (not only in Phase I studies but also in Phase II-III prophylaxis studies), with prophylaxis populations including subjects with varying levels of inherent malaria immunity (non-immune Australian military personnel to semi-immune African residents). In these studies, safety was assessed through vital sign measurements, monitoring of clinical signs/symptoms, physical examinations, clinical laboratory testing, and monitoring of AEs. Selected studies have also included targeted assessments for effects on renal, ocular, pulmonary, or cardiac function, as well as for methemoglobin level.

Table 47: Exposure to tafenoquine and comparators in clinical studies

Study type/ Indication	Controlled studies				Uncontrolled studies	Total Medicine
	Tafenoquine	Placebo	Mefloquine	Primaquine	Tafenoquine	
Clinical pharmacology 050	45	30				75

Study type/ Indication	Controlled studies				Uncontrolled studies	Total Medicine
	Tafenoquine	Placebo	Mefloquine	Primaquine	Tafenoquine	
003 022 TQ-2016-01 014 057 015 040 Study TAF106491	 70 81 	 59 	 	 	32 20 48 34 28 70	32 20 70 48 140 34 28 70
Dose finding 052 051	 18 36	 	 	 12	 	 18 48
Phase I malaria challenge						
Single dose 053	6	6				12
Multiple dose 054 TQ-2016-02	10 16	10 16				20 32
Total	282	121		12	232	
Phase II and III Indication						
Malaria prophylaxis 006 030 033 043 044 045	 205 100 492 109 104 369	 205 100 101 104 	 100 162 140	 	 	 410 300 654 210 208 509
Post-exposure prophylaxis 049	1013			499		1512
Pv treatment	81			34		115

Study type/ Indication	Controlled studies				Uncontrolled studies	Total Medicine
	Tafenoquine	Placebo	Mefloquine	Primaquine	Tafenoquine	
047 058	46			24		70
TOTAL	2519	530	402	557		

* Control = Comparator

7.3.1. Short term exposure dataset Safety of the 200 mg loading dose

The Short-Term Exposure Studies (Table 48) included a total of 12 studies (Studies 003, 006, 014, 022, 040, 043, 047, 049, 050, 052, 053, and 058) that had dosage groups in which tafenoquine was administered to subjects for periods ranging from 1-7 days. Of these 12 studies, there were 6 studies in which a specific dose of tafenoquine was administered as a single dose only (Studies 003, 022, 047, 050, 052, 053), 7 studies where tafenoquine dosing was administered for 3 days (Studies 006, 014, 040, 043, 047, 049, 058), and one study where dosing duration was 7 days (Study 047). Exposure for 4 studies (Studies 006, 043, 049, and 058) utilising these doses is presented in Tables 49-50. In these pooled studies, a total of 491 subjects were exposed to the 200 mg loading dose, while 713 were exposed to the 400 mg loading dose. An additional 161 subjects received 400 mg daily as a split dose of 200 mg BID. The most common adverse events reported in this group are summarised in Table 50 and were similar to the ACR set. The clinical studies that used the ACR and drug exposure are summarised in Table 51.

Table 48: Numbers of subjects exposed to tafenoquine; short-term exposure dataset

	Numbers of Subjects Exposed		
Tafenoquine Dose (mg)	Single Dose Regimen	3-Day Dosing Regimen	7-Day Dosing Regimen
Studies	003, 022, 047, 050, 052, 053	006, 014, 040, 043, 047,049, 058	047
4	5		
16	5		
25	5	80	
36	5		
50	5	86	
72	5		
100	16	82	
144	5		
192	5		
200	46	491	
240	5		
250	5		
288	5		
300	5		18
350	5		
400 once daily 400 given as 200 BID	43 0	635 161	
500	5		
600	27	19	
Total	203	1554	18

Table 49: Short-term studies; tafenoquine drug exposure

	Tafenoquine Dosing Groups				
	Loading Dose Only		Extended Dosing (Loading Dose, then Weekly)		Extended Dosing (Loading Dose, then Monthly)
	200 mg x 3 days	400 mg x 3 days	200 mg x 3 days, then 200 mg weekly (ACR)	400 mg x 3 days, then 400 mg weekly	400 mg x 3 days, then 400 mg monthly
Studies	006, 049	043, 049, 058	030, 033, 043, 045, 057	043	044
n	491	713	825	59	104
Duration of Exposure (weeks)					
Mean (SD)	0.41 (0.19)	0.44 (0.09)	21.22 (8.55)	11.71 (2.68)	17.69 (5.18)
Median	0.40	0.40	26.40	12.4	20.10
Min, Max	0.3, 4.7	0.1, 1.3	0.1, 29.6	0.1, 13.4	0.4, 20.9
Subjects (n, %) with Exposure					
<3 weeks	490 (99.8%)	713 (100.0%)	25 (3.0%)	2 (3.4%)	1 (1.0%)
≥3 and <12 weeks	1 (0.2%)	0	102 (12.4%)	8 (13.6%)	18 (17.3%)
≥12 and <24 weeks	0	0	223 (27.0%)	49 (83.1%)	85 (81.7%)
≥24 weeks	0	0	475 (57.6%)	0	0
Number of Study Doses					
Mean (SD)	3.0 (0.00)	3.7 (1.26)	23.8 (8.60)	14.2 (2.91)	7.4 (1.39)
Median	3.0	3.0	29.0	15.0	8.0
Min, Max	3, 3	1, 6	1, 32	1, 16	3, 8
Completed Prophylactic Phase	491 (100%)	658 (92.3%)	690 (83.6%)	52 (88.1%)	94 (90.4%)

Table 50: AEs reported in the short term used studies

Tafenoquine Loading Dose Administered	200 mg (n=491)	200 mg BID (n=161)	400 mg OD (n=713)
Included Studies	**006, 049**	**049**	**043, 049, 058**
Total Number of AEs	218	115	905
Number of Subjects with at Least One AE	154 (31.4%)	66 (41.0%)	399 (56.0%)
Number (%)of Subjects with Selected AEs			
Gastrointestinal Disorders	102 (20.8%)	63 (39.1%)	323 (45.3%)
Nausea	44 (9.0%)	32 (19.9%)	167 (23.4%)
Abdominal Pain	37 (7.5%)	16 (9.9%)	90 (12.6%)
Diarrhea	25 (5.1%)	24 (14.9%)	82 (11.5%)
Vomiting	4 (0.8%)	5 (3.1%)	29 (4.1%)
GERD	2 (0.4%)	9 (5.6%)	31 (4.3%)
Flatulence	6 (1.2%)	4 (2.5%)	13 (1.8%)
Constipation	2 (0.4%)	0	9 (1.3%)
Nervous System Disorders	29 (5.9%)	13 (8.1%)	109 (15.3%)
Headache	18 (3.7%)	9 (5.6%)	71 (10.0%)
Dizziness	1 (0.2%)	3 (1.9%)	29 (4.1%)
Lethargy	10 (2.0%)	3 (1.9%)	21 (2.9%)
Dysgeusia	0	1 (0.6%)	10 (1.4%)
Infections and Infestations	15 (3.1%)	0	59 (8.3%)
Upper Respiratory Infection	0	0	42 (5.9%)
Nasopharyngitis	5 (1.0%)	0	0
Gastroenteritis	0	0	7 (1.0%)
Wound Sepsis	0	0	7 (1.0%)
General Disorders and Administration Site Conditions	19 (3.9%)	0	13 (1.8%)
Pyrexia	16 (3.3%)	0	7 (1.0%)

Table 50 (continued): AEs reported in the short term used studies

Tafenoquine Loading Dose Administered	200 mg (n=491)	200 mg BID (n=161)	400 mg OD (n=713)
Included Studies	**006, 049**	**049**	**043, 049, 058**
Musculoskeletal and Connective Tissue Disorders	4 (0.8%)	0	28 (3.9%)
Myalgia	0	0	18 (2.5%)
Back Pain	0	0	12 (1.7%)
Arthralgia	3 (0.6%)	0	1 (0.1%)
Eye Disorders	2 (0.4%)	0	22 (3.1%)
Keratopathy	0	0	14 (2.0%)
Conjunctivitis	0	0	4 (0.6%)
Eye Pain	2 (0.4%)	0	0
Blood and Lymphatic System Disorders	1 (0.2%)	0	20 (2.8%)
Eosinophilia	0	0	8 (1.1%)
Thrombocytopenia	0	0	6 (0.8%)
Anemia	0	0	3 (0.4%)
Hemolysis	0	0	2 (0.3%)
Lymphocytosis	1 (0.2%)	0	0
Methemoglobinemia	0	0	1 (0.1%)
Hemolytic anemia	0	0	0
Investigations	1 (0.2%)	0	29 (4.1%)
Blood methemoglobin present	0	0	22 (3.1%)
Eosinophil count increased	0	0	5 (0.7%)
Liver Function test abnormal	0	0	2 (0.3%)
ALT increased	1 (0.2%)	0	1 (0.1%)
AST increased	0	0	1 (0.1%)
Psychiatric Disorders	1 (0.2%)	3 (1.9%)	7 (1.0%)
Insomnia	1 (0.2%)	3 (1.9%)	6 (0.8%)
Mood altered	0	0	1 (0.1%)
Abnormal dreams	0	0	0
Skin and Subcutaneous Tissue Disorders	3 (0.6%)	4 (2.5%)	15 (2.1%)
Rash	2 (0.4%)	2 (1.2%)	4 (0.6%)
Pruritus	0	0	2 (0.3%)
Urticaria	0	0	1 (0.1%)
Ear and Labyrinth Disorders	0	0	1 (0.1%)
Ear pain	0	0	1 (0.1%)
Injury, Poisoning, Procedural Complications	2 (0.4%)	0	8 (1.1%)

Table 51: Drug exposure in studies that utilised the tafenoquine ACR: tafenoquine ACR, placebo, and mefloquine groups

	Tafenoquine 200 mg x 3 days, then 200 mg weekly (ACR)	Placebo	Mefloquine 250 mg x 3 days, then 250 mg weekly
Included Studies	030, 033, 043, 045, 057	030, 043, 044, 045, 057	030, 033, 045
n	825	396	309
Duration of Exposure (weeks)			
Mean (SD)	21.2 (8.6)	10.8 (NA)[a]	18.9 (9.6)
Median	26.4	NA	25.9
Min, Max	0.1, 29.6	0.1, 24.0	0.3, 29.6
Subjects (n, %) with Exposure ≥ 24 weeks	475 (57.6%)	0	158 (51.1%)
Number of Study Doses			
Mean (SD)	23.8 (8.60)	10.7 (NA)	21.6 (9.61)
Median	29.0	NA	28.0
Min, Max	1, 32	1, 27	2, 32

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

7.4.1.1. Integrated safety analyses of the ACR

The most commonly occurring AEs evaluated in 825 subjects receiving the ACR for tafenoquine with an incidence > 10% of subjects that were numerically greater than placebo include gastrointestinal AEs of diarrhoea, gastroenteritis, and nasopharyngitis and the musculoskeletal system AE of back pain (Table 52). When the study of deployed soldiers (Study 033) was not included in the combined analysis of 333 subjects, diarrhoea was no longer of greater incidence when compared to placebo treated subjects.

Table 52: Incidence of adverse reactions in studies of tafenoquine administered as a loading dose of 200 mg daily for three days then weekly up to 6 months in ≥ 10% of patients and numerically greater than placebo

Adverse reaction	Tafenoquine (N=825) 200 mg loading then weekly Studies 030, 033, 043, 045, 057	Tafenoquine (N=333) 200 mg loading then weekly Studies 030, 043, 045, 057	Placebo (N=396) Studies 030, 043, 044, 045, 057
Diarrhoea	105 (12.7%)	16 (4.8%)	23 (5.8%)
Gastroenteritis	209 (25.3%)	26 (7.8%)	17 (4.3%)
Nasopharyngitis	108 (13.1%)	11 (3.3%)	9 (2.3%)
Back pain	116 (14.1%)	47 (14.1%)	26 (6.6%)

AEs occurring in ≥1% of subjects in the tafenoquine ACR group and at a greater incidence than in the placebo group were the following: diarrhoea, GORD, vomiting, chest pain, seasonal allergy, body tinea, motion sickness, keratopathy, gastroenteritis, impetigo, nasopharyngitis,

otitis externa, sinusitis, tinea infection, tinea pedis, tonsillitis, viral infection, arthropod bite, heat illness, joint injury, laceration, ligament sprain, muscle strain, soft tissue injury, thermal burn, arthralgia, back pain, neck pain, lethargy, insomnia, oropharyngeal pain, heat rash, ingrown nail, and rash (Table 53). The incidence of AEs in the combined studies without the study that included deployed soldiers, were lower than when the Study 033 data was included, and in some cases lower than the placebo group.

Table 53: Adverse events occurring in ≥1% of subjects in the tafenoquine ACR group and with an incidence numerically greater than in the placebo group

Adverse reaction	Tafenoquine (N=825) 200 mg loading then weekly Studies 030, 033, 043, 045, 057	Tafenoquine (N=333) 200 mg loading then weekly Studies 030, 043, 045, 057	Placebo (N=396) Studies 030, 043, 044, 045, 057
Gastroenteritis	209 (25.3%)	26 (7.8%)	17 (4.3%)
Back pain	116 (14.1%)	47 (14.1%)	26 (6.6%)
Nasopharyngitis	108 (13.1%)	11 (3.3%)	9 (2.3%)
Diarrhoea	105 (12.7%)	16 (4.8%)	23 (5.8%)
Keratopathy*	68 (8.2%)	0	0
Soft tissue injury	62 (7.5%)	2 (0.6%)	0
Arthralgia	61 (7.4%)	14 (4.2%)	15 (3.8%)
Heat rash	53 (6.4%)	0	0
Viral infection	48 (5.8%)	8 (2.4%)	6 (1.5%)
Laceration	37 (4.5%)	8 (2.4%)	6 (1.5%)
Vomiting	31 (3.8%)	7 (2.1%)	6 (1.5%)
Oropharyngeal pain	30 (3.6%)	18 (5.4%)	12 (3.0%)
Tonsillitis	27 (3.3%)	11 (3.3%)	2 (0.5%)
Rash	25 (3.0%)	5 (1.5%)	2 (0.5%)
Tinea pedis	24 (2.9%)	0	0
Lethargy	24 (2.9%)	1 (0.3%)	0
Motion sickness	21 (2.5%)	0	0
Joint injury	21 (2.5%)	3 (0.9%)	0
Seasonal allergy	20 (2.4%)	1 (0.3%)	0

Adverse reaction	Tafenoquine (N=825) 200 mg loading then weekly Studies 030, 033, 043, 045, 057	Tafenoquine (N=333) 200 mg loading then weekly Studies 030, 043, 045, 057	Placebo (N=396) Studies 030, 043, 044, 045, 057
Chest pain	18 (2.2%)	17 (5.1%)	5 (1.3%)
Body tinea	17 (2.1%)	5 (1.5%)	4 (1.0%)
Sinusitis	17 (2.1%)	5 (1.5%)	2 (0.5%)
Muscle strain	17 (2.1%)	3 (0.9%)	2 (0.5%)
Neck pain	17 (2.1%)	5 (1.5%)	4 (1.0%)
GORD	14 (1.7%)	1 (0.3%)	1 (0.3%)
Thermal burn	10 (1.2%)	1 (0.3%)	0
Insomnia	10 (1.2%)	2 (0.6%)	3 (0.8%)
Impetigo	8 (1.0%)	0	0
Tinea infection	9 (1.1%)	2 (0.6%)	0

GORD= Gastro-oesophageal reflux disorder

7.4.1.2. Other studies

Pooled with the extended dose data set.

7.4.2. Treatment related adverse events (adverse drug reactions)

7.4.2.1. Integrated safety analyses of ACR

The tafenoquine ACR contains data from a number of different types of study populations. Comparisons of specific subgroups within pooled tafenoquine ACR studies allows for the assessment of safety outcomes in subjects who received the tafenoquine ACR with no malaria pre-treatment medications (Studies 033 and 057) versus subjects who received the ACR after pre-treatments (subjects in three African studies; Studies 030, 043, and 045). Also, within the group of subjects who received the ACR, analyses of AEs in deployed military subjects (Study 033) versus non-deployed subjects (Studies 030, 043, 045, and 057) allows for gauging the impact of unique deployment related extrinsic factors.

Overall, the tafenoquine ACR was safe and fairly well tolerated. The majority (73.9%) of AEs in the tafenoquine ACR group were considered 'unrelated' to the study drug. Of the 26.1% of AEs that were considered 'related' to tafenoquine, 399 of 464 (86%) were considered 'unlikely' related. Only 8.6% AEs in the tafenoquine ACR group were considered 'possibly' or 'probably' related to the study drug. No AE was considered 'definitely' related to tafenoquine.

As with primaquine, gastrointestinal AEs (diarrhoea, GORD, vomiting) occurred in subjects who received the tafenoquine ACR. Gastrointestinal AEs rarely lead to discontinuation of tafenoquine dosing. Also, similar to primaquine, tafenoquine showed some risk for haematological AEs, including anaemia, methaemoglobinaemia, and haemolytic anaemia (in individuals with G6PDD). Mild decreases in haemoglobin were seen with tafenoquine exposure, but this effect had no appreciable clinical impact at the doses utilised in the tafenoquine ACR. In only 0.4% of

the ACR population did a decrease in haemoglobin lead to treatment discontinuation; a percentage that was only marginally higher than in the Placebo group (0.3%). In subjects who received the tafenoquine ACR, methemoglobin levels ≥1% were commonly seen but no subject developed levels ≥ 10%. Haemolytic anaemia occurred only rarely in the tafenoquine ACR group, affecting 2 (0.2%) subjects. Overall, no haematological AEs that occurred at an incidence ≥1% in the tafenoquine ACR group had a higher incidence than in the placebo group.

7.4.2.2. Pivotal and/or main efficacy studies

In Study 033 a total of 66 subjects (13.4%) in the tafenoquine group and 19 (11.7%) in the mefloquine group had AEs in the prophylactic phase with a suspected/probable relationship to study treatment. The most commonly reported events were nausea and vertigo (< 3%). No other event occurred in ≥ 2% of subjects in either treatment group.

7.4.3. Deaths and other serious adverse events

7.4.3.1. Integrated safety analyses

In subjects who received the tafenoquine ACR, almost half of all reported AEs were graded as mild (48.6%), while 29.9% were moderate, and 4.0% were severe. No deaths occurred among the tafenoquine ACR population. A total of 49 serious adverse events (SAEs) were reported, affecting 5.7% of subjects; however, only 2.7% of subjects experienced an SAE that was considered 'treatment related' (conservatively defined by the sponsor to include those considered 'unlikely related'). A large proportion of SAEs, 20 of 47, were sporadic infections that affected 1 to 3 subjects with each type of infection. This finding likely reflected the higher risk for infections among deployed military subjects in Study 033. Among the 22 subjects who reported a treatment related SAE, 7 developed an eye disorder, 5 had a decreased GFR, 4 had an infection or infestation, 3 had a gastrointestinal disorder, 2 had a nervous system disorder, and 1 had a blood and lymphatic tissue disorder. Compared with the mefloquine group, subjects in the tafenoquine ACR group experienced lower levels of mild AEs (52.8% mefloquine versus 48.6% tafenoquine ACR). Percentages of subjects with moderate or severe AEs were slightly higher in the tafenoquine ACR group than in the mefloquine group (29.9% versus 26.2% and 4.0% versus 1.6%, respectively). However, 3.3% of subjects in the placebo group also had severe AEs (Table 54).

Table 54: Summary of adverse events by severity; tafenoquine ACR versus placebo and mefloquine

	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=396)	Mefloquine 250 mg daily x 3 days, then 250 mg weekly (n=309)
Included Studies	030, 033, 043, 045, 057	030, 043, 044, 045, 057	030, 033, 045
Total Number of Adverse Events	3496	1298	1445
Mild	3026 (86.6%)	924 (71.2%)	1311 (90.7%)
Moderate	423 (12.1%)	112 (8.6%)	125 (8.7%)
Severe	35 (1.0%)	19 (1.5%)	7 (0.5%)
Missing	12 (0.3%)	243 (18.7%)[a]	2 (0.1%)
Number of Subjects with at Least One AE			
Mild	401 (48.6%)	138 (34.8%)	163 (52.8%)
Moderate	247 (29.9%)	44 (11.1%)	81 (26.2%)
Severe	33 (4.0%)	13 (3.3%)	5 (1.6%)
Missing	11 (1.3%)	63 (15.9%)[a]	0

Although 49 (5.7%) of subjects in the Tafenoquine ACR group experienced an SAE, only 22 (2.7%) of these were considered treatment related. In tafenoquine studies, treatment related AEs were defined very conservatively by the sponsor to include even those AEs that were assessed as 'unlikely' but possibly related to tafenoquine. Among the 22 subjects with treatment related SAEs, the most commonly reported SAE was an eye disorder. Eye disorders accounted for 7 of the 22 treatment related SAEs, with the most frequently reported eye disorder being vortex keratopathy (corneal deposits) (5 subjects). After eye disorders, the next most common treatment related SAE was decreased GFR, which occurred in 5 subjects. Other treatment related SAEs were the following: infections and infestations (4 subjects); gastrointestinal disorders (3 subjects); nervous system disorders (2 subjects) and blood and lymphatic tissue disorders (1 subject). No SAE was considered to be related to tafenoquine in the following categories: Psychiatric disorders; Skin and subcutaneous tissue disorders, or General disorders and Administration site conditions.

7.4.3.2. Pivotal and/or main efficacy studies

A total of 23 subjects experienced SAEs during the prophylactic phase: 18/492 (3.7%) subjects in the tafenoquine group and 5/162 (3.1%) subjects in the mefloquine group. In addition, 10 subjects experienced SAEs during the relapse Follow-up phase; 8/492 (l.6%) subjects in the tafenoquine/placebo group and 2/162 (1.2%) subjects in the mefloquine/primaquine group. In seven subjects (all in the tafenoquine group) the SAEs had a suspected relationship to study treatment. Two subjects had gastrointestinal symptoms: one with abdominal pain and one with abdominal pain and diarrhoea. Five subjects had eye abnormalities; these subjects (specifically vortex keratopathy (corneal deposits)) were in the first cohort in which this eye abnormality was detected during human clinical trials. The randomisation code was broken on these subjects, as well as the three cases of retinal disorder detected at the same time. Because the vortex keratopathy was regarded as a new significant finding, related to tafenoquine treatment, they were reported[11] and became the subject of a 15 day Investigational New Drug (IND) Safety Report. Later safety updates were provided as data became available. Further eye AEs did not meet the criteria for an SAE. Subjects with corneal deposits were followed up beyond the scheduled 3 month Follow-up visit during the relapse Follow up. At each Follow-up, corneal deposits were noted to have improved, with all subjects having resolved within 1 year of stopping study medication.

7.4.4. Discontinuations due to adverse events

7.4.4.1. Integrated safety analyses

In the tafenoquine ACR group, 34 subjects (4.1% of the population) developed an AE that led to treatment discontinuation, compared to 10 subjects (2.5%) of the placebo group. The most common AEs leading to treatment discontinuation were 'Investigations' AEs (11 subjects or 32.4% of all discontinued subjects), including increased ALT (6 subjects), decreased haemoglobin (3 subjects), and decreased glomerular filtration rate (GFR) (2 subjects). Other reasons were unlikely related to study drug and were injuries, poisoning, and procedural complications (6 subjects or17.6% of all discontinued subjects) and infections and infestations (6 subjects or 17.6% of all discontinued subjects).

[11] Sponsor comment: Reported to the Australian HREC, US IRB and TGA as 'unexpected' events.

7.5. Evaluation of issues with possible regulatory impact

7.5.1. Liver function and liver toxicity

7.5.1.1. Integrated safety analyses

Six subjects in the tafenoquine ACR group of Study 045 were discontinued due to ALT elevations, which removed any subject from study participation for any minor ALT elevations. For the overall tafenoquine ACR population, elevations in ALT were reported in 1.5% of the tafenoquine ACR group, which was exactly the same percentage as in the Placebo group. No hepatic SAEs were reported in the tafenoquine ACR group and no hepatic AEs occurred at a frequency ≥1% in that population. For 4 of these 6 subjects, repeat ALT values were available for the period after tafenoquine was discontinued, and all 4 subjects had normalised ALT by study's end.

7.5.2. Renal function and renal toxicity

7.5.2.1. Integrated safety analyses

No renal AEs were reported at incidences ≥1%, in the tafenoquine ACR group. Although decreased GFR was reported as an SAE in 5 (0.6%) subjects in the tafenoquine ACR group, this percentage was comparable to placebo (0.5%). When comparing the tafenoquine ACR to placebo in Study 057 (the targeted 'renal-ocular safety' study), the tafenoquine ACR was equivalent to Placebo (based on not inferiority comparisons) with respect to the study's primary endpoint (mean change from baseline GFR at 24 weeks). Also, no notable differences were observed between the tafenoquine ACR and Placebo for multiple secondary renal endpoints.

7.5.3. Other clinical chemistry

Not applicable.

7.5.4. Haematology and haematological toxicity

7.5.4.1. Integrated safety analyses

Haemoglobin frequently decreases by 0.66 g/dL; about 60% of study participants. In only 3 subjects (0.4% of the ACR population) did a decrease in haemoglobin lead to discontinuation of tafenoquine dosing. This 0.4% percentage was only marginally higher than in the Placebo group (0.3%). Overall, any trend for decline in haemoglobin during tafenoquine dosing had no appreciable clinical impact at the doses utilised in the tafenoquine ACR. A summary of haematological effects is shown in Table 55.

Table 55: Incidence of specific haematological findings: tafenoquine ACR group versus placebo

	Tafenoquine 200 mg x 3 days, then 200 mg weekly (ACR) (n=825)	Placebo (n=396)
Studies Included	**030, 033, 043, 045, 057**	**030, 043, 044, 045, 057**
Number (%) of Subjects with Specific Hematological Findings		
Hemoglobin Decreased ≥0.66 g/dL[a]	496 (60.1%)	166 (41.9%)
Hemolytic anemia[b]	2 (0.2%)	0
Methemoglobin ≥1%	115 (13.9%)[c]	3 (6.0%)
Methemoglobin ≥10%	0	0
Anemia	10 (1.2%)	7 (1.8%)
Leukocytosis	8 (1.0%)	5 (1.3%)
Thrombocytopenia	10 (1.2%)	9 (2.3%)

a Percentages are based on the total number of subjects in the treatment group. b Haemolytic anaemia was defined as a ≥15% decrease from Baseline in haemoglobin or haematocrit, together with a ≥50% decrease from Baseline in haptoglobin. c Only studies 033 and 043 contributed data to the incidence of methemoglobin ≥1%.

As with primaquine, increased methaemoglobin levels can occur with tafenoquine. In normal individuals, enzymes inside RBCs typically maintain physiological concentrations of methaemoglobin at approximately 1 to 2%, and methaemoglobin levels of 1% to 3% are usually asymptomatic. Higher methaemoglobin levels of 3%-15% may also be asymptomatic; however, at levels above 15%, symptoms usually occur. Among subjects who received the tafenoquine ACR, methaemoglobin levels ≥1% were observed in 13.9% of subjects, indicating that methaemoglobin levels may have mildly exceeded the physiological norm. However, no subject developed methaemoglobin levels ≥ 10%.

Haemolytic anaemia occurred only rarely in the tafenoquine ACR group, affecting 2 (0.2%) subjects.

Haematological AEs leading to study discontinuation were decreased haemoglobin, reported in 3 (0.4%) caused by haemolytic anaemia in 2 (0.2%) of subjects in the tafenoquine ACR group. In all 3 withdrawals due to decreased haemoglobin occurred in Study 045 all 3 cases, the decrease in haemoglobin was considered mild and 'non-serious', did not require treatment, and resolved in 28 to 50 days.

Withdrawals dues to haemolytic anaemia occurred in one subject in each of Study 030 and Study 057. Neither subject required treatment and anaemia resolved in both subjects within 1 month. Although 3 haematological AEs occurred at incidences ≥1% in the tafenoquine ACR group (anaemia, leucocytosis, and thrombocytopaenia), none had a higher incidence than in the Placebo group. Similar to what was seen for gastrointestinal AEs, although mild decreases in haemoglobin and mild increases in methaemoglobin were seen in the tafenoquine ACR group, these effects rarely led to discontinuation of tafenoquine dosing.

7.5.5. Other laboratory tests

Not applicable.

7.5.6. Electrocardiograph findings and cardiovascular safety

7.5.6.1. Integrated safety analyses

As an analogue of primaquine, there is the possibility that tafenoquine could share the risk of cardiac side effects of primaquine, including cardiac arrhythmia and prolongation of the QT interval on ECG. Among human subjects who received the tafenoquine ACR (n=825) in 5 pooled clinical trials (Studies 030, 033, 043, 045 and 057) there were no reported cardiac SAEs and no study discontinuations due to cardiac AEs. Furthermore, no cardiac AEs occurred at an incidence ≥1% in subjects who received the tafenoquine ACR. In a non-sponsor clinical study (Study TAF114582, n=260), there was no effect on corrected QT (QTcF) prolongation after a single tafenoquine dose of 300 mg or 600 mg. However, a mean 6.6 ms prolongation of QTcF compared to placebo was seen at 72 hours post-final dose in a group that received a total tafenoquine dose of 1200 mg over 3 days (tafenoquine 400 mg x 3 days).

7.5.7. Vital signs and clinical examination findings

7.5.7.1. Integrated safety analyses

Not applicable.

7.5.8. Immunogenicity and immunological events

7.5.8.1. Integrated safety analyses

Not applicable.

7.5.9. Serious skin reactions

7.5.9.1. Integrated safety analyses

Not applicable.

7.5.10. Other safety parameters

7.5.10.1. Integrated safety analyses

Ocular

Overall, vortex keratopathy (corneal deposits) was reported as an SAE in 0.6% of subjects in the tafenoquine ACR group. In addition, the SAE of 'retinal disorders' occurred in 0.2% of subjects who received the tafenoquine ACR; a slightly lower incidence than was seen in the mefloquine group (0.3%). Eye disorders that occurred at incidences ≥1% in the tafenoquine ACR group were conjunctivitis and vortex keratopathy (corneal deposits). Conjunctivitis occurred at a lower incidence (2.9%) than in the placebo population (4.5%).

Vortex keratopathy was noted in early clinical studies of tafenoquine at daily doses higher than the 200 mg daily employed in the Tafenoquine ACR. Subsequently, 74 of the 492 subjects in the tafenoquine ACR group of Study 033 underwent more detailed ophthalmic assessments, specifically examining for vortex keratopathy. Fundoscopic examinations revealed abnormalities (such as granularity/pigmentation of retinal pigment epithelium, hard drusen) in 27 of 69 (39.1%) tafenoquine ACR subjects and in 4 of 17 (23.5%) of mefloquine subjects. Vision was not affected in any of these individuals. Among the subjects with retinal findings, fundus fluorescein angiograms (FFA) were performed in 15 of the 31 cases and were considered abnormal in 4 of 14 (28.6%) of the tafenoquine ACR subjects and in 1of 1 (100%) mefloquine subjects. By the end of the study's prophylactic period, 69 (93.2%) of the 74 subjects known to have developed keratopathy. However, there were no changes in tests of visual fields, visual acuity, or colour vision in these subjects, and all subjects experienced complete resolution of their vortex keratopathy (corneal deposits) within 1 year after the end of tafenoquine dosing. An expert ophthalmology advisory board reviewed the ophthalmologic findings from Study 033 and concluded that the observed corneal changes were benign and fully reversible. As a follow-up to Study 033, Study 057 was designed to assess the ophthalmic safety of the Tafenoquine ACR compared to placebo. Although there was no evidence in this study that exposure to tafenoquine had an adverse effect on the retina, treatment-emergent corneal changes in one or both eyes were observed in a greater proportion of subjects receiving the Tafenoquine ACR (21.4%) than in subjects receiving placebo (12.5%). They did not impact vision, and they resolved within 1 year in all cases.

Neuropsychiatric

Nervous system disorders of headache, dizziness, or lethargy affected ≥1% of the tafenoquine ACR population; however, only lethargy occurred at a higher incidence (2.9%) than in the Placebo group (0%). Motion sickness was reported in 21 (2.5%) subjects in the tafenoquine ACR population. All these cases occurred among deployed military personnel in Study 033. The subjects' deployment could have influenced their risk for this AE, as it is a recognised problem among mobilised military populations. Also, the use of concomitant antiparasitic medications (albendazole and ivermectin) in this study could have contributed to causing or exacerbating motion sickness.

One psychiatric AE occurred at an incidence ≥1% in the tafenoquine ACR group. This was insomnia, which affected 1.2% of subjects in the tafenoquine ACR group. Because the comparator drug mefloquine carries a risk for psychiatric side effects, the AE profile of tafenoquine was examined in greater depth for AEs that occurred at low incidences <1%. Overall, subjects in the tafenoquine ACR group and the mefloquine group had comparable incidences of these relatively rare psychiatric AEs, and both of these groups had higher incidences of rare psychiatric AEs than did Placebo subjects. Rare psychiatric AEs that occurred

in tafenoquine ACR subjects but not in the Placebo group included: abnormal dreams sleep disorder, nightmare, depression, agitation, anxiety disorder, euphoric mood, bipolar disorder, depressed mood, neurosis, panic attack, stress and suicide attempt.[12] Of these, the majority affected only 1 or 2 subjects. Notably, both the tafenoquine ACR group and the mefloquine group included military populations in Study 033 that were exposed to hostile environments, which may have increased their risk for psychiatric AEs. There was also no placebo group in Study 033;[13] so the incidence of rare psychiatric AEs in the tafenoquine (and mefloquine) groups cannot be compared to placebo to determine their relative incidence.

A review of psychiatric AE data from Study 033 revealed that subjects in that study had a unique psychiatric AE profile compared to subjects in other Tafenoquine ACR studies. They also reported much higher rates of deployment related injuries, which were ultimately captured in the safety database as AEs in the tafenoquine ACR group (almost all of these AEs were assessed as 'not related' to tafenoquine). Unique deployment related psychological stressors and combat related injuries were among the influential 'extrinsic factors' to which subjects in Study 033 were exposed but which did not affect subjects in other tafenoquine ACR studies. The influence of deployment related extrinsic factors on the military population of Study 033 is evidenced by differences in the AE profile of tafenoquine in that study versus other tafenoquine ACR studies. Deployed ADF subjects had a higher incidence of AEs compared to non-deployed subjects for all AE categories.

7.6. Other safety issues

7.6.1. Safety in special populations

7.6.1.1. Adolescent Subjects

Dosing regimens consisted of the following: single dose only (Studies 036 and 047); 3 day loading dose regimens (Studies 006 and 043); a 2 week regimen (Study 047); and loading doses followed by extended weekly dosing (Studies 030 and 045). The highest daily dose by weight (11.2 mg/kg) was received by a 17 year old male (in Study 047) who was administered a 500 mg single dose and who experienced abdominal discomfort and loose stools, both of which resolved. One adolescent was withdrawn from the clinical studies due to an AE with potential relationship to tafenoquine, an elevated ALT (151 U/L) at Day 31 after receiving low dose tafenoquine (25 mg/day x 3 days then weekly) in Study 045. In Study 036, the single young girl who received tafenoquine (dose 15 mg or 1 mg/kg) in that study developed 'moderate' methaemoglobinaemia (11%) on Study Day 2, which increased to 14.5% on Day 4, and 17.8% on Day 7. The girl also showed mild dizziness and mild cyanosis of the lips and fingernails on Day 4 that resolved spontaneously within 1 day. The study was suspended to allow investigation of the ophthalmic findings in Study 033 soon after. So, the numbers involved do not raise any red flags or give us sufficient data to make any conclusions.

Study 006 included a population of 216 adolescents (ages 12 to 17) who received tafenoquine loading doses of 25, 50, 100, or 200 mg daily x 3 days. The safety findings also were satisfactory, with no withdrawals or SAEs related to tafenoquine. Although rates of non-serious AEs increased with increasing tafenoquine dosage, there was no clear dose relationship for individual AEs, except possibly for abdominal pain (which might be anticipated based on the known gastrointestinal AE profile of tafenoquine).

[12] Sponsor comment: The suicide attempt was deemed unrelated to tafenoquine by the study investigator. See the PI (Attachment 1).
[13] Sponsor comment: Due to the ethics of exposing a non-immune population to malaria in a war-like theatre.

7.6.1.2. Geriatric subjects

Only one subject over age 65 received tafenoquine in any of the sponsor's clinical trials. She successfully completed the study and experienced no adverse events.

7.6.1.3. Race/ethnicity

Tafenoquine safety data were not segregated by race/ethnicity.

7.6.1.4. Glucose-6-phosphate dehydrogenase (G6PD) deficiency

G6PDD individuals are at risk of haemolysis when exposed to tafenoquine. Although almost all tafenoquine studies have excluded subjects with G6PDD, 8 subjects with G6PDD or other haemoglobinopathies were inadvertently recruited in 5 of the tafenoquine clinical trials and received tafenoquine regimens. Many of the subjects showed no signs or symptoms of haemolysis, and any who were symptomatic ultimately recovered, typically after receiving outpatient oral treatments. Only one subject (Study 043) required hospitalisation and transfusions. This subject had received 400 mg tafenoquine in the 3 day load only group, a dose that is twice that of the 200 mg loading dose used in the tafenoquine ACR. Some of these subjects had initial negative genotypic testing for G6PD and were phenotypically negative. The only study specifically designed to investigate the use of tafenoquine in people with G6PDD (Study 001) did not recruit and was abandoned.

7.6.1.5. Psychiatric history

Early clinical trials of tafenoquine did not exclude subjects based on previous psychiatric history. However, once it was identified that mefloquine carried a risk for psychiatric AEs any tafenoquine trial with a mefloquine comparator included a psychiatric exclusion. There were 6 subjects with known or suspected psychiatric history at baseline among 21 clinical trials of tafenoquine prior to 2013. Four of these subjects experienced neuropsychiatric AEs, while two subjects did not. In 3 of these 4 cases the AE was considered to be either unrelated or remotely related to tafenoquine. One episode of psychosis was considered 'possibly' related to tafenoquine, although the subject had an undisclosed history of two prior psychiatric admissions.

7.6.1.6. Effect of military deployment

For specific AEs, the increased incidence in deployed ADF subjects versus non-deployed subjects was evident for: motion sickness (4.3% versus 0%); gastroenteritis (37.2% versus 7.8%), nasopharyngitis (19.7% versus 3.3%), tinea pedis (4.9% versus 0%), diarrhoea (18.1% versus 4.8%), soft tissue injury (12.2% versus 0.6%), joint injury (3.7% versus 0.9%), laceration (5.9% versus 2.4%), joint injury (3.7% versus 0.9%), muscle strain (2.8% versus 0.9%), arthropod bite (2.4% versus 0.6%), heat illness (2.2% versus 0%), thermal burn (1.8% versus 0.3%), insomnia (1.6% versus 0.6%), and abnormal dreams or nightmares (1.6% versus 0%). Overall, the AE profile of deployed ADF subjects who received the Tafenoquine ACR reflected the impacts of the following extrinsic factors: the subjects' susceptibility to travellers' illnesses (gastroenteritis, diarrhoea, nasopharyngitis); the jungle setting (tinea pedis, heat illness, arthropod bite); physical encounters with a hostile enemy (soft tissue injury, laceration, joint injury, muscle strain, thermal burn), and the stress of peacekeeping operations (insomnia, abnormal dreams, nightmares). These findings are consistent with evidence from other studies in military populations that showed that the adverse effect profiles of antimalarial drugs were negatively impacted by deployment, especially combat deployment.

7.6.2. Safety related to drug-drug interactions and other interactions

No specific data reported.

7.7. Post marketing experience

None reported.

7.8. Evaluator's overall conclusions on clinical safety

From the safety data provided it appears that the most common side effects seen in the group treated with tafenoquine (compared to placebo) were gastrointestinal: diarrhoea, GORD, vomiting, which did not require drug discontinuation. Other AEs reported were unlikely to be related to study drug and more likely to be related to the conditions/context of the studies, such as ear pain, motion sickness, vortex keratopathy (corneal deposits), chest pain, seasonal allergy, body tinea, gastroenteritis, impetigo, nasopharyngitis, back pain. Gastrointestinal side effects appear to be the most common treatment related AEs and are more common with higher doses.

Ocular changes, particularly and asymptomatic, vortex keratopathy (corneal deposits), were also seen in Study 057, but were not serious and resolved.

The biggest potential safety issue, as with primaquine, seems to be the potential for haemolytic crisis in patients with G6PDD. This group was largely excluded from these studies, but the use of tafenoquine in people genetically more likely to have this deficiency. Neuropsychiatric adverse events were recorded in a small number of subjects (mainly in Study 033), but most were not thought to be related to study drug. There were no other red flag AEs, but the safety data group is not very large.

Post-marketing safety data will be important and there is none available yet. There is no data for more than 26 weeks of use.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

Table 56: Assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
An effective weekly drug for prophylaxis against malaria during potential exposure in endemic countries. Evidence of post-exposure prophylaxis. Efficacy against malaria generally and specifically against both Pv and Pf. Efficacy has been shown in different populations in different geographical locations. Does not seem to have the AEs related to the other weekly malaria prophylaxis option (mefloquine). Has good post-exposure efficacy due to long half-life. Side effects similar to primaquine.	There is good data in non-immunes who took this drug regularly weekly (in Australian army volunteers). There is also good data for efficacy in two regions (studies conducted in Thailand and Ghana). A number of the other studies also showed good efficacy but had different dosages and regimens. Also, some studies had major logistical and reliability problems (such as with the malaria smears). The neuropsychiatric side effects seen with mefloquine are not seen with Tafenoquine generally, although there were some reported in Study 033 (conducted on ADF personnel during deployment). A number of the studies were conducted 1 to2 decades ago and the standards may be different to studies conducted more

Indication	
Benefits	**Strengths and Uncertainties**
	contemporaneously. There are no studies comparing this drug against malarone (now a commonly used malaria prophylaxis drug) and rapidly replaced mefloquine as standard of care.[14] No data about the long-term ocular effects of long term use (past 26 weeks).

8.2. First round assessment of risks

Table 57: Assessment of risks

Risks	Strengths and Uncertainties
Studies have been on small numbers and a number of them conducted decades ago. Compliance in army studies has been very high; this may not be so in reality. No post-marketing data. No local background malaria incidence data to really assess what kind of impact tafenoquine would have. Because of the long half-life, the loading dose is important otherwise blood levels may not be sufficient by the time of exposure (one week after starting). It is also important for post-exposure prophylaxis, that one dose is taken after leaving the endemic area. Gastro-intestinal side effects are quite common, particularly diarrhoea (13% of subjects), GORD (2%), and vomiting (4%). This drug is contra-indicated in people with G6PDD, but may also have adverse haematological effects in other people as well. Haemoglobin frequently decreases by 0.66 g/dL. Methaemoglobin characteristically increases to >1% but does not increase to as much as 10%, a level associated with hypoxia. In Study 033, vortex keratopathy (corneal deposits) occurred in ≥8% of tafenoquine subjects.	Post-marketing data needs to be submitted to further assess the incidence of potentially serious side effects, particularly haematological and ocular. Gastrointestinal AEs can be ameliorated to some extent by taking tafenoquine with food. There were no changes in tests of visual fields, visual acuity, or colour vision in these subjects, and all subjects experienced complete resolution of their vortex keratopathy (corneal deposits) within 1 year after the end of tafenoquine dosing. Vortex keratopathy (corneal deposits) resolved by the Week 48 follow-up visit in all Tafenoquine ACR subjects.

[14] Sponsor comment: Malarone is given daily. Mefloquine is given weekly. Malarone was not approved for chemoprophylaxis when these studies were conducted.

8.3. First round assessment of benefit-risk balance

This assessment is very difficult to make. Statistically Study 033 achieved its primary outcome, that tafenoquine was non-inferior to mefloquine. This prophylactic efficacy was also shown in Study 045 (in semi immunes in Africa). The well conducted challenge Study TQ-2016-02 reinforces the efficacy of tafenoquine against the asexual stages of malaria (but obviously is not a comparable environment or duration). Overall, the benefit-risk balance of tafenoquine for the proposed usage is favourable.

Tafenoquine is a drug that fills a gap in relation to malaria prophylaxis need. It may prove to be very useful, as a once weekly option. It does not have the neuropsychiatric side effects that mefloquine does, but it does have potential for serious haematological side effects and the ocular side effects also need to be studied further in the RMP. There is also no post-marketing data to confirm safety or data past 26 weeks. It would also be ideal to see some studies comparing tafenoquine to malarone, which is being increasingly used (but does require daily therapy).

Although, on balance, the evaluator thinks this drug fills a need, there is a need for more safety data, particularly in relation to use in heterozygotes for G6PD and the ocular side effects. There should be an undertaking to collect this.

9. First round recommendation regarding authorisation

Whilst it would be nice to see the licensing of a new drug that obviously has efficacy against malaria and allows weekly rather than daily dosing, the evaluator thinks that more data is needed.

10. Clinical questions

10.1. General

1. Could the sponsor please provide an update on the status of the USA submission and the queries raised?

10.2. Pharmacokinetics and pharmacodynamics

2. In the initial challenge studies used to determine a dosing structure, it is stated that a plasma concentration >50 ng/mL was thought to be adequate to prevent relapse. Why was the goal of 80 ng/mL then chosen as the desired minimal concentration?
3. Given that a number of these studies were conducted over a decade ago (some 2 decades), it would be very helpful to have a timeline with a summary of the various dosing regimens (and resultant decision making for subsequent trial design).
4. Has any consideration been given to a malaria challenge study such as Study TQ-2016-2 being performed with Pv?

10.3. Efficacy

5. Could the sponsor please provide data on malaria related morbidity and mortality in Australia?

11. Second round evaluation

11.1. General

11.1.1. Question 1

Could the sponsor please provide an update on the status of the USA submission?

Evaluator's assessment

This submission has not yet been approved in the USA, and interestingly, similar to Australia, the TGA had concerns about the lack of statements relating to GCP for some of the studies. The company does not state whether they have provided these statements either to the USA or the TGA (and they are not included in the documentation).

11.2. Pharmacokinetics and pharmacodynamics

11.2.1. Question 2

In the initial challenge studies used to determine a dosing structure, it is stated that a plasma concentration >50 ng/mL was thought to be adequate to prevent relapse. Why was the goal of 80 ng/mL then chosen as the desired minimal concentration?

Sponsor response

Studies in non-immune persons, showed that symptomatic breakthrough of malaria occurred when tafenoquine plasma concentrations were < 50 ng/mL. Consequently, a precautionary plasma concentration of 80 ng/mL was selected as the minimum target trough value for prevention of symptomatic malaria development in non-immune individuals

Evaluator's assessment

The specific question is not answered.

11.2.2. Question 3

Given that a number of these studies were conducted over a decade ago (some 2 decades), it would be very helpful to have a timeline with a summary of the various dosing regimens (and resultant decision making for subsequent trial design).

Sponsor response

The Phase II studies that led to the generation of the proposed clinical regimen were Studies 053 and 054, 006, 044, and 043.

- Studies 053 and 054 (study reports in 2004) were small challenge studies provided pharmacokinetic data that allowed some correlation of parasitological failure with trough drug levels.
- Study 006 (study report in 2002) investigated different loading doses and found that dose levels of 50 mg to 200 mg were equally protective for 7 weeks, suggesting that for prolonged prophylaxis, a loading dose would have to be supplemented with maintenance doses.
- Study 044 (study report in 2003) investigated a complete prophylactic regimen (loading dose followed by maintenance doses) with 400 mg.
- Study 043 (study report in 2003) was the study which utilised the submitted clinical regimen. Both 200 mg per dose or 400 mg per dose were equivalent and 200 mg better tolerated.

Phase III studies consisted of Studies 045, 033, and TQ-2016-02.

- Study 045 (study report in 2003) was the first study that compared the proposed clinical regimen (200 mg/day x 3 days followed by 200 mg weekly) to the active comparator mefloquine (in semi-immunes).
- Study 033 (study report in 2008) compared the proposed clinical regimen to the active comparator mefloquine in non-immunes predominately exposed to Pv.
- Study TQ-2016-02 (study report in 2017) was performed to expand the database with respect to Pf.

The table below summarises the studies submitted.

Table 58: Studies submitted with this submission

Study #	Design	Tafenoquine Dosing	Year of study report
Phase 2 prophylactic studies			
053	Challenge	600 mg once	2004
054	Challenge	[various]	2004
006	Loading doses in semi-immunes	25 mg to 200 mg per day x 3 days	2002
044	Loading dose in mixed immunes	400 mg per day x 3 days followed by 400 mg monthly	2009
043	Full prophylactic regimens (loading plus maintenance doses) in semi-immunes	200 mg/day or 400 mg/day x 3 days followed by 200 mg or 400 mg weekly	2003
Phase 3 prophylactic studies			
045	Full prophylactic regimens compared to mefloquine in semi-immunes	Full prophylactic regimens (25 mg/dose to 200 mg/dose) compared to mefloquine	2003
033	Full prophylactic regimens compared to mefloquine in non-immunes	Full prophylactic regimen (based on 200 mg/dose) compared to mefloquine	2008
TQ-2016-02	Full prophylactic regimen compared to placebo in *P. falciparum* blood stage challenge	Full prophylactic regimen (based on 200 mg/dose) compared to placebo	2017
***Pv* treatment study**			
058	Treatment of symptomatic *P. vivax* infection	400 mg per day x 3 days, compared to standard treatment with chloroquine and primaquine	2007

Evaluator's assessment

This timeline does make things slightly clearer and sets out the information in a much better way than it was in the original submission. But, not all the studies in the submission are included in the summary response or the table; for example Studies 047, 049, TAF112582 and 030. This also highlights that the initial submission was not well organised.

The table also is quite misleading as the studies look more recent and contemporary when stating the year of the 'Study Report' rather than the Study time period. Studies 053 and 054 for instance, were conducted in 1997 but in the table above it states the year of the report as 2004 (7 years later). Study 033 was conducted in 2000-2001, Study 045 in 1998, Study 043 in 1997 and Study 058 in 2005. It is also unclear why some study reports were written up to 7 years after the study.

11.2.3. Question 4

Has any consideration been given to a malaria challenge study such as Study TQ-2016-2 being performed with Pv?

Sponsor response

The response discussed Study 058 (which was conducted 13 years ago), in which patients symptomatic with Pv infection were treated with 400 mg/day x 3 days. The response states that from this study, one could extrapolate the theory that, given that presenting parasitemia prior to tafenoquine treatment was 8,000 parasites/µL, whereas only 0.06 parasites/µL blood (for a person with 5L blood volume) exit the liver to initiate blood stage infection, Study 058 signifies that the proposed tafenoquine clinical regimen will be effective against the relatively low Pv parasite burden present in the blood during prophylaxis. In essence, Study 058 substitutes for a Pv challenge study, so no challenge study is planned for Pv.

Evaluator's assessment

This rationale is theoretical but probably correct for prophylaxis, although the concentration of drug used in Study 058 was different to the one in this submission (400 mg not 200 mg). This issue is not addressed.

11.2.4. Question 5

Could the sponsor please provide data on Malaria related morbidity and mortality in Australia?

Evaluator's assessment

This response is adequate but when the evaluator tried to look up the WHO reference provided it did not work. When the evaluator looked up the WHO World Malaria report 2014 accessed at http://www.who.int/malaria/publications/world_malaria_report_2014/wmr-2014-no-profiles.pdf?ua=1 on 3 March 2018, the numbers were so low for Australia in 2013 that no transmission and no deaths were recorded on the report. On searching the document, the only time that Australia is mentioned in the report is in relation to financial contribution to malaria control.

Overall, the evaluator thinks that the numbers provided show that malaria exposure and prophylaxis impacts upon small numbers in Australia but, in certain populations, it can become a significant problem. This population also has significant reason to avoid mefloquine. This is still however, no data about the use of Malarone in this population, which would abrogate the need for compliance with post-deployment prophylaxis for weeks (as need with mefloquine or doxycycline).

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

There is only one additional benefit that can be documented from the additional information. Up to 5% of ADF personnel returning to Australia after deployment to South-East Asia develop malaria, probably due to compliance problems with compliance with current post-exposure prophylaxis regimens (mefloquine and doxycycline). Tafenoquine has potential to prevent this with one post-exposure dose according to the data presented.

12.2. Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of tafenoquine are unchanged from those identified in the first round evaluation (see above).

12.3. Second round assessment of benefit-risk balance

The changes recommended below should be adopted.

12.4. Second round recommendation regarding authorisation

The ADF data about the risk of malaria in returned ADF personnel is the strongest argument so far for the licensing of this drug in Australia. Unfortunately, there is still no comparative data with Malarone. The evaluator would however support licensing of tafenoquine for use in military personnel (or other personnel at high risk of malaria) in whom other, licensed prophylaxis drugs are contra-indicated or not tolerated (this would require a change in the wording of the indication).

13. References

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Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au