60PH04 Long Term Safety Protocol

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29Nov2018

Multisite, Randomized, Double Blind, Placebo-Controlled Study to Assess the Long-Term Safety of Tafenoquine

Protocol Number: 60PH04

Sponsor:	**60° Pharmaceuticals LLC**
Version number:	**Version 7.0**
Date:	**29Nov2018**

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Investigator Signature Page

Multisite, Randomized, Double Blind, Placebo-Controlled Study to Assess the Long-Term Safety of Tafenoquine

(Version 7.0, 29Nov2018)

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to personally conduct or supervise the study.

The study will be conducted in accordance with the principles set out in the following documents:

- The most recent version of the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants;
- National Statement on Ethical Conduct in Human Research (NHMRC 2007a, updated May 2015);
- Notes for Guidance on Good Clinical Practice – Annotated with Comments (CPMP/ICH/135/95), as adopted by the Australian Therapeutic Goods Administration (TGA) (July 2000); and
- The current Clinical Trial Protocol as approved by the local Human Research Ethics Committee (HREC), Institutional Review Board (IRB) and the USAMRMC Human Research Protection Office (HRPO).

I agree to inform all participants that the study drug is being used for investigational purposes and I will ensure that the requirements related to obtaining informed consent are in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice (GCP) Section 4.8 (CPMP/ICH/135/95) and local requirements.

I agree to report adverse events (AEs) that occur in the course of the study to the sponsor in accordance with ICH GCP Section 4.11 and local requirements.

I have read and understand the information in the 60P Investigator's Brochure (IB), including the potential risks and side effects of the study drug.

I agree to promptly report to the HREC any changes in the research activity and all unanticipated problems involving risk to the participants. I will not make any changes to the conduct of the study without the HREC, IRB, HRPO and sponsor approval, except when necessary to eliminate apparent, immediate harm to participants.

I agree to maintain adequate and accurate records and make those records available in accordance with ICH GCP Section 4.9 and local requirements.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

I understand that the study may be terminated or enrollment suspended at any time by the sponsor, with or without cause, or by me if it becomes necessary to protect the best interest of the participants.

Site Principal Investigator

_____ Date: _____

Dr Fred Chen
Lions Eye Institute

Site Principal Investigator

_____ Date: _____

Dr Mark Chittum

Retina Consultants of Southern Colorado

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_____

Dr. Victor Gonzalez

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Signature

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List of Non-Standard Abbreviations and Definitions

Abbreviation	Definition
β-HCG	Beta-human chorionic gonadotropin
^{14}C	Carbon-14
60P	60° Pharmaceuticals LLC
Ab	Antibody
ABN	Australian business number
Recommended Regimen	Anticipated clinical regimen
ADF	Australian Defence Force
ADL	Activity of daily living
ADR	Adverse drug reactions
AE	Adverse event
AESI	Adverse event of special interest
AFS	Awake following sleep
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AM	Ante meridiem- before noon
ANZCTR	Australia New Zealand Clinical Trials Registry
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BCVA	Best corrected visual acuity
BDC	Bile duct cannulated
BFW	Behavior following wakening
BUN	Blood urea nitrogen
CAD	Color assessment and diagnosis
CBC	Complete blood count
CD	Curative dose
CD_{50}	The dose of a therapeutic agent that radically cures 50% of the target pathogen
CDC	Centers for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of federal regulations
CI	Confidence interval
CIDI	Composite international diagnostic interview
CIOMS	Council for International Organizations of Medical Sciences

Abbreviation	Definition
CL/f	The apparent systemic clearance from plasma following extravascular administration
C_{max}	The observed maximum plasma concentration following drug administration
CNS	Central Nervous System or Clinical Network Services (CNS) Pty Ltd
CPMP	Committee for Proprietary Medicinal Products
CQ	Chloroquine
CRO	Clinical research organization
CSF	Central sub field
C-SSRS	Columbia - Suicide Severity Rating Scale
CTCAE	Common terminology criteria for adverse events
CTN	Clinical trial notification
CYP	A member of the cytochrome P450 gene family
DDE	Drug dictionary enhanced
DHI	Dizziness handicap inventory
DICOM	Digital imagery and communications in medicine
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data and safety monitoring board
DSUR	Drug safety update report
DVC	DynPort Vaccine Corporation
EC	European Commission
ECG	Electrocardiogram
eCRF	Electronic case report form
ED_{50}	The dose of a therapeutic agent that eradicates 50% of the target pathogen
EDMS	Electronic data management system
EDTA	Ethylene diamine tetra-acetic acid
EMA	European Medicines Agency
EOS	End of study
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
FAF	Fundus auto fluorescence
FBC	Full blood count (as known as complete blood count [CBC])
FCSR	Final clinical study report
FDA	US Food and Drug Administration

Abbreviation	Definition
FEV_1	Forced expiry volume in 1 second
FFA	Fundus fluorescein angiogram
FLS	Forward light scatter
FM	Farnsworth-Munsell
FSH	Follicle stimulating hormone
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good clinical practice
GGT	Gamma glutamyl transpeptidase
GI	Gastrointestinal
GMP	Good manufacturing practice
GP	General practitioner
GTS	Getting to sleep
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCQ	Hydroxychloroquine
Hct	Hematocrit
HCV	Hepatitis C virus
HCVA	High contrast visual acuity
hERG	Human ether-a-go-go related gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRA	Heidelberg retina angiograph
HREC	Human research ethics committee
HRPO	Human research protection office
IAW	In accordance with
IB	Investigator's Brochure
IC_{50}	The half maximal inhibitory concentration of a particular drug or substance
ICD	International classification of diseases
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
ILM	Internal limiting membrane
IMP	Investigational medicinal product
IND	Investigational new drug

Abbreviation	Definition
IOP	Intraocular pressure
IRB	Institutional review board
ISCEV	International Society for Clinical Electrophysiology of Vision
ISS	Integrated safety summary
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive web response system
ka	First order absorption rate constant
LCVA	Low contrast visual acuity
LLN	Lower limit of normal
LMM	Local medical monitor
logCS	Logarithm of contrast sensitivity
logMAR	Logarithm of minimum angle of resolution
LSEQ	Leeds sleep evaluation questionnaire
M.I.N.I	Mini international neuropsychiatric interview
MAIA	Macular integrity assessment
MATE1	Multidrug and toxin extrusion 1 transporter
MATE2-K	Multidrug and toxin extrusion 2-K transporter
MCH	Mean corpuscular hemoglobin
MCT	Mesopic contrast threshold
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MetHb	Methemoglobin
ms	Millisecond
N or n	Number
NHMRC	National Health and Medical Research Council
NI	Non-inferiority
OCT	Optical coherence tomography
OCT2	Human organic cation transporter 2
P. berghei	*Plasmodium berghei*
P. cynomolgi	*Plasmodium cynomolgi*
P. cynomolgi bastianelli	*Plasmodium cynomolgi bastianelli*
P. falciparum	*Plasmodium falciparum*
P. fragile	*Plasmodium fragile*

Abbreviation	Definition
P. vivax	*Plasmodium vivax*
PCFR	Patient clinical/fetus report
pH	Power of hydrogen
PI	Principal investigator
PIICF	Participant information and informed consent form
PIC/S	Pharmaceutical inspection cooperation scheme
PK	Pharmacokinetic
Plt	Platelet count
PM	Post meridiem – after noon
PP	Per protocol
PSPMO	Pharmaceutical Systems Project Management Office
PT	Preferred term
PXR	Pregnane-X-receptor
QD	quaque die (once per day)
qFAF	Quantitative fundus auto fluorescence Also termed quantitative auto fluorescence
QOS	Quality of sleep
QT	Interval measured from the start of the Q wave to the end of the T wave (time taken for ventricular depolarization and repolarization)
QTc	Corrected QT interval
RBC	Red blood cell
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SCID-P	Structured clinical interview for diagnostic and statistical manual of mental disorders
SCT	Scotopic contrast threshold
SD	Standard deviation
SD-OCT	Spectral domain optical coherence tomography
SDTM	Study data tabulation model
SOC	System organ class
SOP	Standard operating procedure
SOSE	Serious ophthalmic safety event
SSI	Significant safety issue

Abbreviation	Definition
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	The terminal elimination half-life
TD	Time domain
TBS	TGA business services
TEAE	Treatment emergent adverse event
TGA	Australian Therapeutic Goods Administration
TNFα	Tumor necrosis factor alpha
ULN	Upper limit of normal
UPIRTSO	Unanticipated problems involving risks to participants or others
USAMMDA	US Army Medical Materiel Development Activity
USAMRMC	US Army Medical Research and Materiel Command
USM	Urgent safety measure
UV	Ultraviolet
V/f	Volume of distribution
VA	Visual acuity
WBC	White blood cell
WHO	World Health Organization
WHO-DDE	WHO Drug dictionary enhanced
WOCBP	Women of child bearing potential

Study Synopsis

Name of Sponsor:	60° Pharmaceuticals LLC
Name of Investigational Product:	Tafenoquine succinate
Study Title:	Multisite, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Long-term Safety of Tafenoquine
Protocol Number:	60PH04
Local CRO Australia:	Clinical Network Services (CNS) Pty Ltd Level 4, 88 Jephson Street Toowong, QLD, 4066, Australia Tel: +61 7 3719 6000 Email: cns@clinical.net.au
Local CRO United States:	Fast-Track Drugs & Biologics, LLC 5 Paramus Ct. North Potomac, MD 20878 Tel: 301-762-5787 Email:jransom@fasttrackresearch.com
Study Centers:	Linear Clinical Research, Australia; Lions Eye Institute, Australia Retina Consultants of Southern Colorado, Colorado Springs, CO, USA Valley Retina Institute, McAllen, TX, USA
Site Principal Investigators:	Dr Fred Chen, Lions Eye Institute Dr. Mark Chittum, Retina Consultants of Southern Colorado Dr. Victor Gonzalez, Valley Retina Institute
Study Period:	August 2017 to August 2020
Purpose and Objectives:	Primary objective: • To assess the ophthalmic safety of tafenoquine after 12 months of exposure versus placebo using Spectral Domain Optical Coherence Tomography (SD-OCT) and Quantitative Fundus Auto Fluorescence (qFAF). Secondary objective: • To assess the long-term safety and tolerability of tafenoquine versus placebo as assessed by clinical monitoring of vital signs, ECG, laboratory data, and reporting of Adverse Events (AEs) after 12 months of exposure. • To assess the long term safety and tolerability of tafenoquine after 12 months of exposure to tafenoquine versus placebo by measuring ophthalmic and psychiatric changes from baseline to end of study.
Study Design:	This randomized, double-blind, placebo controlled study will involve 600 healthy (Glucose-6-Phospate Dehydrogenase [G6PD] normal) volunteers and

	will run over two phases. *Part 1 – Treatment Phase (52 weeks, Week 1, 4, 12, 24, and 52)* Participants who meet the eligibility criteria will be randomized (ratio 1:1) using clinical site as a randomization variable to receive a loading dose of either tafenoquine 200 mg (2 x 100 mg tablets) or placebo daily for three consecutive days, followed by study treatment (tafenoquine 200 mg or placebo) once per week for 51 weeks, with safety follow-up visits at Weeks 4, 12, 24, and 52. A Columbia Suicidality Rating Scale (C-SSRS) Interview will be conducted at the Day 1 visit and every 4 weeks ± 1 week thereafter. All efforts will be made to retain participants through to study completion. Reasons for withdrawal may include 1) withdrawal of consent, 2) lost to follow-up, 3) evidence of substance abuse that may affect the participant's capacity to complete the study in the investigator's opinion and 4) development of a new or worsening psychiatric disease (including suicidal ideation) at a non-scheduled visit or during routine M.I.N.I. evaluation that would jeopardize the safety of the participant if they continued in the study (see Section 9.2.7). If a participant stops taking their study drug, they should still continue to have all follow-up safety visits. If the subject wants to withdraw, they should have an end of study (EOS) visit (preferably 65-75 days after cessation of study treatment). The reasons for any treatment discontinuation (temporarily or permanently) will be documented on the electronic Case Report Form (eCRF). *Part 2 – Follow-up Phase (Week 64)* Due to the long t1/2 of tafenoquine (13-15 days with an expected 65-75-day washout period), all participants will return to the clinic at Week 64 for their EOS visits. If the participant has an ongoing AE, they will continue in Part 3 of the study, otherwise this is the final visit. *Part 3 – Follow-up Phase (Weeks 76, 89, and 104).* Participants who meet the criteria for continuation for additional safety assessments at the Week 64 visit will continue to be assessed for up to 3 more times at approximately 12-week intervals or until resolution or stabilization of the AE whichever is earlier.
Endpoints:	Primary endpoint: • Proportion of participants with protocol-defined serious ophthalmic safety event (SOSE). SOSE is assessed by significant retinal changes from baseline using SD-OCT and qFAF. The details of significant protocol defined retinal changes using SD-OCT and qFAF are defined in Table 5. Secondary endpoints: • The incidence, severity and relationship to the investigational medicinal product (IMP) of AEs (including unexpected toxicities, AEs encountered during or after IMP administration), safety laboratory parameters, vital signs, and ECG, up to and including Week 64. • Mean change from baseline in key SD-OCT parameters including central subfield thickness (CST), total macular volume (TMV), and parafoveal (inner ring of Early Treatment Diabetic Retinopathy Study [ETDRS] grid), retinal thickness and the proportion of participants with ellipsoid or interdigitating zone disruption (as per Table 5). • Proportion of participants with abnormal changes from baseline

	observed on qFAF using the Spectralis Heidelberg Retina Angiograph (HRA)+OCT device with grey scale values extracted from these images for statistical analysis using qFAF software (Heidelberg Engineering). • Mean change from baseline in Best Corrected Visual Acuity (BCVA). • Proportion of participants with corneal deposits from slit lamp examination of the corneal epithelium. • Time to onset of corneal deposits and overall time duration to resolution post treatment start. • Time duration to resolution of corneal deposits after treatment cessation. • Proportion of participants with new abnormalities compared with baseline observed with color retinal digital photography (conventional and wide field). • Proportion of participants with new abnormalities compared with baseline observed with microperimetry. • Proportion of participants with any new anomaly on the backlit ETDRS chart. • Proportion of participants with any clinically significant change in ETDRS BCVA (defined as ≥15 letter change [≥ 3 lines] of change in ETDRS BCVA at 4 meters) • Proportion of participants who develop a color deficiency using the Farnsworth-Munsell 100 (FM-100) hue test. • Proportion of participants who develop a loss of 0.12 or greater logarithm of contrast sensitivity (logCS) on the Mars letter contrast sensitivity test. • Proportion of participants who develop a psychiatric disorder in accordance with the Diagnostic and Statistical Manual of Mental Disorders Version 5 (DSM-5) as assessed with the Mini International Neuropsychiatric Interview (M.I.N.I.) 7.0.2 assessment questionnaire and suicidal ideation or suicide attempt by C-SSRS interview. • Proportion of participants with an AE of dizziness or vertigo and severity as assessed by the Dizziness Handicap Inventory (DHI). • Mean change from baseline scores in Getting to Sleep (GTS), Quality of Sleep (QOS), Awake Following Sleep (AFS), and Behavior Following Wakening (BFW) as assessed by the Leeds Sleep Evaluation Questionnaire (LSEQ).
Sample Size (planned):	The study will involve 600 healthy (G6PD normal) volunteers (300 on tafenoquine and 300 on Placebo) and will run over three parts. The primary endpoint is the proportion of participants with protocol-defined SOSE. SOSE is assessed by significant retinal changes from baseline using SD-OCT and qFAF at any follow-up visit. The details of significant protocol defined retinal changes using SD-OCT and qFAF are defined in Table 5. Sample size estimation is based on the primary endpoint. Based on the binomial distribution, if the true SOSE rate is assumed to be 1% in the tafenoquine group, there is a 95% probability to observe at least one SOSE with 300 participants. This study could therefore also be considered a non-inferiority (NI) safety

	study. The incidence of SOSE was conservatively assumed to be 1% (i.e., 99% without SOSE) for both the placebo and tafenoquine group. A non-inferiority margin of 2.5% (treatment-placebo, in terms of SOSE rates) was considered to be clinically relevant, and therefore used to compare the non-inferiority between tafenoquine and placebo. The 2.5% NI margin is estimated from literature. On an Australian population scale, the prevalence of maculopathy is 1.3% in age cohorts 49-54 years with increasing prevalence in cohorts aged 55-64 (2.6%), 65-74 (8.5%), 75-84 (15.5%), and 85+ (28.0%) years (Mitchell 1995). The 2.5% NI margin sets a lenient threshold to determine if tafenoquine causes retinal deficits beyond what is expected even in a high-risk group at the upper age range of 55 years for the study population. That is, if the SOSE rate for tafenoquine group is not more than 2.5% higher than the placebo, the safety for tafenoquine will be regarded as no worse than placebo. For a two-sided significance level of 5% (α=0.025 one-sided) with 600 randomized subjects, the power is 86% (β=0.14) to test the non-inferiority margin.
Study duration:	Each participant will participate for up to 25 months: Screening period – 6 weeks; Exposure period – 12 months; and Follow-up period – 3 months or until AE resolution (up to 12 months).
Investigational Medicinal Products:	Investigational Medicinal Products: Tafenoquine and matched placebo, manufactured under contract by the US Army Medical Research and Materiel Command (USAMRMC), will be supplied by 60° Pharmaceuticals LLC in tablet form for oral administration. Each tablet will contain 100 mg tafenoquine. The dose to be administered is 200 mg (two tablets) per day for three consecutive days (loading doses), followed by another 200 mg dose once per week for the following 51 weeks (beginning post-loading dose Day 10). Control participants will receive identically matched double-blind placebo tablets under the same schedule.
Main Inclusion Criteria:	Participants eligible for inclusion in this study must fulfill all of the following criteria: 1. Completion of the written informed consent process (signed). 2. Male or female age 18 to 55 years inclusive, in good health as assessed by the investigator. 3. Normal G6PD enzyme activity levels as defined by the parameters of the specific G6PD test employed at the local laboratory. 4. Negative Hepatitis B surface antigen (HBsAg) and Hepatitis C virus (HCV), Human Immunodeficiency Virus (HIV)-1, HIV-2 antibody screen at the screening visit. 5. Negative serum pregnancy test. 6. Women of Child Bearing Potential (WOCBP) agree to use an acceptable method of contraception from the time of the first administration of the IMP until 12 weeks following last administration of the IMP or have undergone a sterilization procedure or are post menopausal. Acceptable birth control methods include: a. Oral contraceptives (combination estrogen/progesterone pills), injectable progesterone or sub dermal implants (commenced at least 14 days prior to IMP administration to the female participant)

	b. A medically prescribed topically applied transdermal contraceptive patch (commenced at least 14 days prior to IMP administration to the female participant); c. Intrauterine device or intrauterine system; d. Partner uses condom with spermicide; e. Male partner has had a vasectomy (more than 3 months previously) f. True abstinence: when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent participants (in consultation with their partners) have to agree to use one of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 90 days after the last dose of study drug. Acceptable sterilization procedures include: g. Essure® sterilization; h. Bilateral tubal ligation; i. Hysterectomy; j. Bilateral oophorectomy; or, k. Be postmenopausal with amenorrhea for at least 1 year prior to screening and confirmed by a serum Follicle Stimulating Hormone (FSH) test at screening. 7. Willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures. 8. Agree to stay in contact with the study site for the duration of the study and up to 2 weeks following the EOS visit, provide updated contact information as necessary, and have no current plans to move away from the study area for the duration of the study.
Safety, Tolerability, Ophthalmic, Neurologic and Psychiatric Assessments:	Safety evaluations will include the following: AE evaluation, physical examination, vital signs, ECG, laboratory parameters (hematology, biochemistry, and urinalysis). These will be performed at various time points throughout the study to assess baseline function and any changes from baseline after administration of IMP during the Treatment Phase. **Screening, -6 Weeks to Day -1 (Visit 1a/1b)** • Informed consent. • Inclusion and exclusion criteria. • Demographics. • Body height and weight. • Medical, surgical and social histories. • Prior medications. • Full physical examination as defined in the protocol. • Vital signs (sublingual body temperature, respiratory rate, pulse rate, systolic and diastolic blood pressure). • 12-lead electrocardiogram (ECG). • Blood sampling for determination of the following parameters: o Complete blood count (CBC) (Hematology [platelet count {Plt}, red blood cell {RBC} count, hemoglobin (Hb), hematocrit {Hct}, mean corpuscular volume {MCV}, mean corpuscular hemoglobin {MCH}, white blood cell {WBC} count with differential [neutrophils, lymphocytes, monocytes, eosinophils and basophils]);

	○ Biochemistry (blood urea nitrogen [BUN], creatinine, potassium, sodium, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], gamma glutamyl transpeptidase [GGT], total and direct bilirubin); ○ G6PD activity; ○ Methemoglobin (MetHb)%; ○ Serology: HIV-1 and HIV-2, HCV, HBsAg; ○ Serum pregnancy test (females): (serum beta-human chorionic gonadotropin) [β-HCG]) or FSH test (for post-menopausal females). • Alcohol breath test. • Urine sampling for determination of the following parameters: ○ Urinalysis (specific gravity, power of hydrogen [pH], glucose, protein, blood, ketones, leukocyte esterase, and nitrites). Microscopic examination (if blood, leukocyte esterase or nitrites are positive). ○ Urine drug screen (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tetrahydrocannabinols, tricyclic antidepressants); • Psychiatric Assessments: ○ M.I.N.I. English Version 7.0.2. **Screening, -6 Weeks to Day -1 (Visit 1b).** Note that 1a and 1 b visits can be split over two or more days, but the ophthalmologic assessments can be conducted at the 1a visit after other screening procedures are completed at the discretion of the clinical site in the order most convenient to the site and study subject: • Ophthalmic assessments (before pupil dilation): ○ BCVA (ETDRS letter score); ○ Color vision assessment with FM-100 hue test; ○ Mars letter contrast sensitivity test; ○ M-chart distortion test; and ○ Slit lamp examination. • After pupil dilation: ○ Macular Integrity Assessment (MAIA) microperimetry. Conducted twice with the first result discarded to minimize learning effect; ○ Heidelberg Spectralis SD-OCT (including wide field macular scan); ○ Heidelberg Spectralis qFAF (set of 3 images to ensure consistency in measurement); ○ Digital photograph of corneal surface (conventional and wide field); ○ Digital photograph of retina (conventional and wide field); and, ○ Slit lamp retinal examination (pupils dilated) and intraocular pressure (IOP) measurement. **IMP Loading Dose: Week 1, Day 1 (Visit 2)** • Confirmation of consent/signed informed consent. • Update information regarding any new medical conditions, medicines (including herbal products and nutritional supplements), surgery or illnesses since screening. • C-SSRS to update suicidal ideation since screening MINI.

	• Update information on social history since screening.
	• Abbreviated physical examination (pre-dose).
	• Vital signs.
	• Blood sampling for determination of the following parameters:
	  o CBC and biochemistry;
	  o MetHb%; and
	  o PK analysis for tafenoquine.
	• Urine sampling for determination of the following parameters:
	  o Urine pregnancy test (β-HCG) (pre-dose, WOCBP participants only);
	  o Urinalysis (specific gravity, power of hydrogen [pH], glucose, protein, blood, ketones, leukocyte esterase, and nitrites). Microscopic examination (if blood, leukocyte esterase or nitrites are positive); and
	  o Urine drug screen (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tetrahydrocannabinols, and tricyclic antidepressants).
	• Alcohol breath test.
	• Psychiatric Assessments
	  o DHI (only collected if participant reports AE of dizziness or vertigo); and
	  o LSEQ assessment.
	• Recording AEs and any concomitant medications;
	• Inclusion/exclusion criteria confirmed,
	• Randomize subject using IWRS using clinical site as a randomization variable; and
	• Dispense IMP and provide instructions on use of diary card and training on electronic compliance system.
	Part 1 - Treatment Phase, Week 4 to Week 52 (Visits 3, 4, 5, and 6):
	• Abbreviated physical examination for Weeks 4, 12 and 24
	• Vital signs.
	• 12-lead ECG (Weeks 4 and 52 [Visits 3 and 6]).
	• Blood sampling for determination of the following parameters:
	  o CBC and biochemistry;
	  o MetHb %; and
	  o PK blood collection for tafenoquine.
	• Urine sampling for determination of the following parameters:
	  o β-HCG urine screen (WOCBP only);
	  o Urinalysis (specific gravity, pH, glucose, protein, blood, ketones, leukocyte esterase, and nitrites). Microscopic examination (if blood, leukocyte esterase or nitrites are positive); and
	  o Urine drug screen (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tetrahydrocannabinols, and tricyclic antidepressants).
	• Ophthalmic Assessments (before pupil dilation):
	  o BCVA (ETDRS letter score);
	  o Color vision assessment with FM-100 hue test;
	  o Mars letter contrast sensitivity test;
	  o M-chart distortion test; and

	○ Slit lamp examination and corneal deposit grading (the Orlando system). • After pupil dilation: ○ MAIA microperimetry; (only Weeks 24 and 52); ○ Heidelberg Spectralis SD-OCT (including wide field macula scan); ○ Heidelberg Spectralis qFAF (set of 3 images to ensure consistency in measurement); ○ Digital photograph of corneal surface (conventional and wide field); ○ Digital photograph of retina (conventional and wide field); • Slit lamp retinal examination and IOP measurement. • Psychiatric Assessments: ○ M.I.N.I. English Version 7.0.2 at Weeks 12, 24 and 52; ○ DHI (only collected if participant reports AE of dizziness or vertigo); and ○ LSEQ. • AEs. • Concomitant medications. • Electronic compliance system, diary cards and used blister packs checked. Diary cards and final used blister packs collected at Week 52. **Part 1 – Treatment Phase – Every 4 Weeks** • C-SSRS interview will be conducted every 4 weeks ± 1 week. The interview can either be conducted by telephone or in person at a clinic visit. **Part 2 – EOS Follow-up Phase, Week 64 (Visit 7a and 7b) Note assessments can be distributed over one or more days at the convenience of the site and subject:** • Full physical examination as defined in the protocol. • Vital signs (sublingual body temperature, respiratory rate, pulse rate, systolic and diastolic blood pressure). • 12-lead ECG. • Blood sampling for determination of the following parameters: ○ CBC and biochemistry. ○ MetHb%. ○ Serum pregnancy test (β-HCG) (WOCBP participants only). • Urine sampling for determination of the following parameters: ○ Urinalysis (specific gravity, pH, glucose, protein, blood, ketones, leukocyte esterase, and nitrites). Microscopic examination (if blood, leukocyte esterase or nitrites are positive). ○ Urine drug screen (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tetrahydrocannabinols, tricyclic antidepressants); • Ophthalmic Assessments (before pupil dilation): ○ BCVA (ETDRS letter score); ○ Color vision assessment with FM-100 hue test; ○ Mars letter contrast sensitivity test; ○ M-chart distortion test; and ○ Slit lamp examination and corneal deposit grading (the

	Orlando system). • After pupil dilation: o MAIA microperimetry; o Heidelberg Spectralis SD-OCT (including wide field macula scan); o Heidelberg Spectralis qFAF (set of 3 images to ensure consistency in measurement); o Digital photograph of corneal surface (conventional and wide field); o Digital photograph of retina (conventional and wide field); o Slit lamp retinal examination and IOP measurement; and • Psychiatric Assessments: o M.I.N.I. English Version 7.0.2 at Weeks 12, 24 and 52; o DHI (only collected if participant reports AE of dizziness or vertigo); o LSEQ; and, o C-SSRS – every 4 weeks ± 1 week after the Week 52 Visit • AEs. **Part 3 - Follow-up <u>Ongoing AEs</u> Weeks 76, 89, and 104 (Visits 8, 9 and 10) every 3 months until resolution (out to 12 months post final study drug dose – visits will only be scheduled if an AE was ongoing at a prior visit):** • 12-lead ECG • Blood sampling. • CBC and biochemistry; and • MetHb%. • Urinalysis (specific gravity, pH, glucose, protein, blood, ketones, leukocyte esterase, and nitrites). Microscopic examination (if blood, leukocyte esterase or nitrites are positive). • Ophthalmic assessments, including selected ophthalmic examination, microperimetry, BCVA (EDTRS), FM-100 hue testing, Mars letter contrast sensitivity test, M-chart and qFAF to follow only specific, abnormal results. • Psychiatric assessments: o M.I.N.I. English Version 7.0.2. (If required to follow-up an AE or disorder). o DHI (if AE reported by participant); and • Any other AE. For compliance confirmation during the dosage phase – plasma samples will be taken at Weeks 1, 4, 12, 24, and 52. There is no specific timing for obtaining the pharmacokinetic (PK) sample during each scheduled visit. The date and time of the PK sample is to be recorded in the eCRF. Date, time, and number of tablets recorded in participant diary cards and/or electronic compliance management system will also be transferred to the eCRF. Drawing of blood samples is estimated to be 135 mL/participant within the trial prescribed procedures and will not exceed 275 mL for the entire study period (Appendix 3).
Statistical analysis:	<u>Safety population:</u> All participants who received study treatment at least once will be included in the safety population. This is the primary population for safety and tolerability analysis. <u>Intention-to-Treat (ITT) population:</u> The ITT population will consist of all

	participants as they are randomized to the study. Primary and secondary ophthalmic endpoints will be analyzed by ITT population. In this non-inferiority setting, analysis based on ITT population provides supportive evidence to analyses based on Per Protocol population. Per Protocol (PP) population: All participants who received at least 25% of the total planned dose for IMP, had at least one valid baseline and post baseline evaluation by SD-OCT and qFAF, and had no major protocol deviations will be included in the PP population. This is the primary population for the primary safety endpoint analysis and other secondary ophthalmic endpoints. Though this is a safety study, all subjects will be analyzed in the treatment group to which they were randomized. Detailed aspects of the analysis will be presented in the statistical analysis plan (SAP), which will be finalized prior to breaking of the study blind and database lock. In general, for safety analyses, descriptive statistics will be tabulated by treatment group for all participants. Unless otherwise stated, all safety analyses will use the Safety population. The analysis of AEs will consider only AEs occurring for the first time, or worsening, during or after the first administration of study medication. The analysis will focus on incidence of AEs in the treatment groups, although for AEs of special interest, the number of events will also be provided (i.e. ophthalmic assessments). Tables summarizing AEs will be displayed by preferred term and system organ class (SOC). Analysis of Serious Adverse Events (SAEs) and the categorization of AEs by severity and relationship to study medication will also be included. AEs leading to study withdrawal or deaths on-study will also be presented in tables and/or listings. Treatment-emergent changes in vital signs and laboratory parameters will be presented using tabulations by group. Descriptive statistics for each parameter and/or the change from baseline at each time point will be provided. For endpoints measured on a categorical scale the number of participants and percentages will be provided. **Primary Endpoint Measures** The primary endpoint for the safety of tafenoquine versus placebo is measured by SOSE rate, as assessed by SD-OCT and qFAF parameters. A detailed list of SD-OCT and qFAF parameters assessed in this study is presented in Appendix 1 and Appendix 2. Clinically significant changes for quantitative measures will be defined as a change from baseline by a threshold taken from previously published coefficient of repeatability (Table 5). For qualitative assessments, new findings or worsening of findings from baseline exams regarded to be of clinical importance will be considered a change from baseline. If either of the automated reading (CST or TMV) is missing or deemed unreliable; the pericentral (inner ring) retinal thickness will be used to impute the missing data. Descriptive summary tables will be produced showing the results by each eye and across both eyes, for each assessment (including follow-up). Data from repeated tests carried out due to abnormal values will not be tabulated. All data, including those from repeat tests, will be provided in a listing. For this primary endpoint, a participant will be considered to have a clinically significant SOSE if any of the five parameters listed in Table 5 indicates a change from baseline in either eye at any time point during treatment. The 95% confidence intervals (CI) of SOSE rate will be calculated by treatment group, using the Clopper Pearson Exact methodology for the proportion of

	participants who did experience a clinically significant deterioration. The risk difference of the SOSE rates between tafenoquine and placebo will be estimated. The upper limit of two-sided 95% CI for the risk difference will be compared against the protocol pre-specified NI margin. **Secondary Endpoint Measures** • The incidence, severity and relationship to the IMP of AEs will be summarized at ≥1% (common) and ≥10% (very common) level. Safety laboratory parameters and vital signs up to and including the EOS visit (Week 64) will be summarized descriptively. • Mean change from baseline in key SD-OCT parameters including CST, TMV, and parafoveal (inner ring of ETDRS grid) retinal thickness and the proportion of participants with ellipsoid or interdigitating zone disruption (Table 5). The difference in the proportion of participants with clinically significant ophthalmologic changes (as defined in the primary endpoint) between treatment group and the placebo group in each of SD-OCT parameters will be calculated. In addition, the change from baseline in individual SD-OCT and qFAF parameters listed in Appendix 1 and Appendix 2 will be tabulated and compared between tafenoquine and placebo-treated groups. • Proportion of participants with abnormal changes from baseline observed on qFAF using the Spectralis HRA+OCT device with grey scale values extracted from these images for statistical analysis using qFAF software (Heidelberg Engineering). • Mean change from baseline in BCVA. Changes from baseline in BCVA results by the ETDRS chart will be tabulated and compared between the two groups. A clinically significant deterioration is defined as a reduction of more than 4 letters from baseline (Week 1, Day 1 [Visit 2]) of 0.08 logMAR. The M-chart will be used to quantify the severity of the distortion (if detected). An additional analysis of BCVA changes will include the proportion of participants experiencing a 1-4 letter change (less than one line of ETDRS visual acuity change), a 5-9 letter change (1 line, but less than 2-line change), 10-14 letter change (2 lines, less than 3 lines) or 15 or more letter change (3 lines or more) in BCVA from baseline. A three line or more change in ETDRS BCVA at 4 meters is considered clinically significant. • Proportion of participants with corneal deposits from slit lamp examination of the corneal epithelium. Severity of corneal deposits by impairment of vision: The proportion of participants with grades I to IV corneal deposits and with impairment on any of the vision tests will be tabulated for each time point for each eye and overall. For participants with corneal deposits identified from slit lamp examination, the time to first onset and time to resolution after treatment cessation will be tabulated. Corneal structural changes are defined as changes from Baseline (Week 1, Visit 2) of two or more grades of corneal changes. These data will also be provided in a listing. • Time to onset and resolution of corneal deposits after treatment cessation.

	• Proportion of participants with new abnormal changes from baseline observed with color retinal digital photography (conventional and wide field). • Proportion of participants with new abnormal changes from baseline observed with microperimetry. • Proportion of participants who develop a loss of 0.12 or greater logCS on the Mars letter contrast sensitivity test. • Proportion of participants with any new anomaly on the backlit ETDRS chart. • Proportion of participants who develop a new color deficiency using the FM-100 hue test. • Retinal changes (structural) and the impact on macular function (functional) will be tabulated for each time point for each eye. The macular function tests include BCVA (EDTRS), FM-100 hue test, M-chart, and microperimetry. Clinically significant changes in any of the results of all five tests will be counted as having an impact on macular function. Retinal abnormalities on fundoscopy, digital fundus photography (conventional and wide field), SD-OCT and qFAF at Screening are considered to be structural changes but may not affect macular function with 12 months of treatment with tafenoquine. • The proportion of participants with retinal abnormalities identified from digital photographs (conventional and wide field) will be tabulated for each time point and overall. These data will also be provided in a listing. • Proportion of participants who develop a new psychiatric disorder in accordance with the DSM-5 as assessed with the M.I.N.I. 7.0.2 assessment questionnaire and suicidal ideation or suicide attempt by C-SSRS interview. • Proportion of participants with an AE of dizziness or vertigo and severity as assessed by the DHI. • Mean change from baseline in GTS, QOS, AFS, and BFW as assessed by the LSEQ. For the above secondary safety endpoints, the proportion of participants with a type of abnormal change or new abnormal change will be compared by a Fisher's exact test between tafenoquine and placebo. The 95% CI of the abnormality rate will be summarized by Clopper Pearson Exact methodology. A logistic regression will be used to compare the risk of having the abnormality (odds ratio and 95% CI) between tafenoquine and placebo. For time to event safety endpoint, a log-rank test will be used to compare the time to onset/resolution of the event between tafenoquine and placebo. Cox regression will be used to compare the risk of having the safety endpoint (hazard ratio and 95% CI) between tafenoquine and placebo. Change from baseline in BCVA, key SD-OCT continuous parameters (Table 5) and LSEQ component scores will be analyzed by a random intercept mixed model to account for correlation between repeated measures. Treatment effect (difference and 95% CI) on the change from baseline variables will be estimated across study visits.

1. STUDY SCHEDULE OF EVENTS

Study Phase	**Screening**		**Treatment (Week 1 to Week 52)**					**Phase 2 Follow-up**		**Phase 3 follow-up (ongoing AEs at end of Phase 2)**		
Week	**-6 Weeks to Day -1**		**Week 1, Day 1**	**Week 4 ±3 days**	**Week 12 ±2 weeks**	**Week 24 ±2 weeks**	**Week 52 ± 2 weeks**	**Week 64 ±2 weeks (EOS)**		**Week 76 ± 2 weeks**	**Week 89 ± 2 weeks**	**Week 104 ± 2 weeks**
Visit Number	**1a/ 1b[a]**		**2**	**3**	**4**	5	**6**	**7a/7b[b]**		**8**	**9**	**10**
Written informed consent	X		X[c]									
Randomization			X									
Inclusion & exclusion	X		X									
Demographics	X											
Body height and weight	X											
Medical, surgical & social history	X		Update									
Prior medications[d]	X		Update									
Physical examination[e]	X		X	X	X	X	X	X				
Vital signs[f]	X		X	X	X	X	X	X				
12-lead ECG	X			X			X	X		Repeat if needed to follow AE		
Hematology/ biochemistry[g]	X		X	X	X	X	X	X		Repeat if needed to follow AE		
G6PD testing	X											
Methemoglobin (MetHb%)	X		X	X	X	X	X	X		Repeat as needed to follow AE		
Serology[h]	X											
Pregnancy test[i]	X		X	X	X	X	X	X				
PK blood collection for tafenoquine[j]			X	X	X	X	X					

Study Phase	**Screening**		**Treatment (Week 1 to Week 52)**					**Phase 2 Follow-up**		**Phase 3 follow-up (ongoing AEs at end of Phase 2)**		
Week	**-6 Weeks to Day -1**		**Week 1, Day 1**	**Week 4 ±3 days**	**Week 12 ±2 weeks**	**Week 24 ±2 weeks**	**Week 52 ± 2 weeks**	**Week 64 ±2 weeks (EOS)**		**Week 76 ± 2 weeks**	**Week 89 ± 2 weeks**	**Week 104 ± 2 weeks**
Visit Number	**1a/ 1b**[a]		**2**	**3**	**4**	5	**6**	**7a/7b**[b]		**8**	**9**	**10**
Alcohol breath test	X		X									
Urinalysis (dipstick) and urine drug screen[k]	X		X	X	X	X	X	X		Repeat urinalysis only if needed to follow AE		
Ophthalmic assessments (before dilation: BCVA (ETDRS letter score FM-100 hue test, MARS letter contrast sensitivity test, M-Chart and slit lamp examination/grading of deposits after Screening. (After dilation: SD-OCT, qFAF, digital photograph of cornea, retina (conventional and wide field), slit lamp retinal exam and IOP measurement		X			X	X	X		X	Repeat if needed to follow AE		
Microperimetry[l]		X				X	X		X	Repeat if needed to follow AE		
MINI 7.0.2	X				X	X	X	X		Repeat if needed to follow AE		
DHI			Only collected if participant reports AE of dizziness or vertigo							Repeat if needed to follow AE		
LSEQ			X	X	X	X	X	X				
C-SSRS			X	Every 4 weeks ± 1 week								
AE collection			X	X	X	X	X	X		Repeat if needed to follow AE		
Concomitant medication			X	X	X	X	X	X				
IMP administration			200 mg daily x 3 days Week 1, then 200 mg once/week through to Week 52									

Study Phase	**Screening**		**Treatment (Week 1 to Week 52)**					**Phase 2 Follow-up**		**Phase 3 follow-up (ongoing AEs at end of Phase 2)**		
Week	**-6 Weeks to Day -1**		**Week 1, Day 1**	**Week 4 ±3 days**	**Week 12 ±2 weeks**	**Week 24 ±2 weeks**	**Week 52 ± 2 weeks**	**Week 64 ±2 weeks (EOS)**		**Week 76 ± 2 weeks**	**Week 89 ± 2 weeks**	**Week 104 ± 2 weeks**
Visit Number	**1a/ 1b**[a]		**2**	**3**	**4**	5	**6**	**7a/7b**[b]		**8**	**9**	**10**
Diary cards and blister packs issued/ checked/ collected			X	X	X	X	X					

[a] Note that 1a and 1 b visits can be split over two or more days, but the ophthalmologic assessments can be conducted at the 1a visit after other screening procedures are completed at the discretion of the clinical site in the order most convenient to the site and study subject

[b] Note that the 7a and 7b visits can be conducted over multiple days and arranged at the convenience of the site and subject within the visit window.

[c] Review prior to dosing with IMP.

[d] 28-days before date of first IMP including herbal supplements and nutritional supplements.

[e] Full physical exam at Screening (Visit 1a) and at Week 64 (Visit 7a). Abbreviated physical exam to be conducted for the remainder of the study visits.

[f] Blood pressure, pulse rate, respiratory rate and sublingual body temperature after the participant has been sitting for 5 minutes.

[g] Hematology and biochemistry include tests listed in Section 9.2.4 Laboratory evaluations.

[h] Including HBsAg antigens and HCV, HIV-1 and HIV-2 antibodies.

[i] Serum pregnancy test (ß-HCG) will be done in all WOCBP at Screening (Visit 1a) and Week 64 (Visit 7a). Urine pregnancy tests will be performed prior to the first dose of IMP and all other time points. FSH test may be substituted for a ß-HCG test to confirm menopausal status (females only).

[j] PK samples may be taken at any time during the visit.

[k] Urinalysis (specific gravity, pH, glucose, protein, blood, ketones, leukocyte esterase, and nitrites). Microscopic examination (if blood, leukocyte esterase or nitrites are positive). Urine drug screen (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tetrahydrocannabinols, tricyclic antidepressants).

[l] Microperimetry will be conducted at Screening (Visit 1b) twice (first result discarded to minimize learning effects) then repeated at Week 24 and 64 (Visits 5 and 7b).

2. INTRODUCTION

2.1. Background

Five species of the malaria *Plasmodium* parasite infect humans, with *P. falciparum* and *P. vivax* being the most common and deadly. *Plasmodium* has a complex lifecycle with different forms in both the mosquito and humans (CDC 2016a). The pathogenesis of malaria has been well described (Kim 2013). When an individual is bitten by an infected mosquito, unicellular *Plasmodium* sporozoites enter the blood and are rapidly transported to the liver. There the sporozoites enter hepatocytes, where they develop into schizonts, each containing ~30,000 merozoites per hepatocyte. After 6 to 16 days, the schizonts burst and the daughter merozoites are released into the bloodstream and infect susceptible red blood cells (RBCs). These parasitized RBCs (approximately 1-20 RBCs per µL of blood) become sticky and clump, blocking capillaries in various parts of the body, including vital organs (WHO 2015). Also, within the RBCs, merozoites develop rapidly into schizonts, and after 48 to 72 hours they release a new wave of merozoites into the circulation, accompanied by lysis of RBCs. The release of tumor necrosis factor alpha (TNFα) and inflammatory cytokines produces high fever and the direct destruction of RBCs results in anemia. In severe cases, potentially fatal neurological manifestations of cerebral malaria, renal, hepatic, pulmonary and circulatory failure occur (Wattavidanage 1999). Worldwide, over 1 million deaths occur each year due predominantly to falciparum malaria. In Africa alone, almost 3,000 children die from malaria each day (Johns Hopkins 2016).

In malaria due to *P. vivax* or *P. ovale*, dormant parasitic forms termed “hypnozoites” can remain in hepatocytes for weeks to years, ultimately giving rise to a distinct disease episode after the primary attack (“relapsing” malaria) (Kim 2013). Consequently, malaria due to *P. vivax* or *P. ovale* can produce significant morbidity during these relapses. *P. vivax* malaria is a neglected disease that is an important public health issue in many parts of the world. This form of malaria caused an estimated 13.8 million cases globally in 2015, and accounted for about half of all malaria cases outside of Africa (WHO 2015).

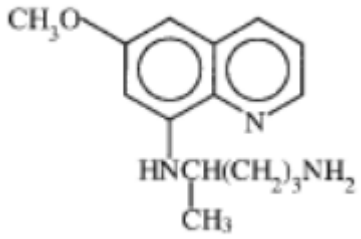
In the non-immune population, those without previous exposure to and recovery from malaria, infection with *P. falciparum* or *P. vivax* is a medical emergency since it can lead to severe complications and death. The US Centers for Disease Control and Prevention (CDC) recommends malaria chemoprophylaxis for US persons travelling to malaria endemic regions when there is sufficient risk of contracting *Plasmodium* infection (CDC 2016b). As of 2015, the CDC-recommended malaria chemoprophylactic regimens for regions where chloroquine-resistant *P. falciparum* exists included the following drugs: atovaquone-proguanil, doxycycline, mefloquine (CDC 2016b). Additionally, primaquine has also been used in prophylaxis of malaria, but is not US Food and Drug Administration (FDA)-approved for this indication (CDC 2016b). None of these regimens is optimal on the basis of efficacy, tolerance, and convenience/compliance (Castelli 2010). For malaria chemoprophylaxis, the unmet medical need is for an effective drug that can be administered weekly and does not have the adverse side effects of other antimalarials (Dow 2015).

Tafenoquine [2, 6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy) primaquine, succinate] is a primaquine analog, with a long half-life of approximately 13-15 days (Figure 1) (Brueckner 1998). Tafenoquine under the trade name of ARAKODA™ was approved by the US FDA for the prophylaxis of malaria in adults in August 2018. Tafenoquine under the tradename of

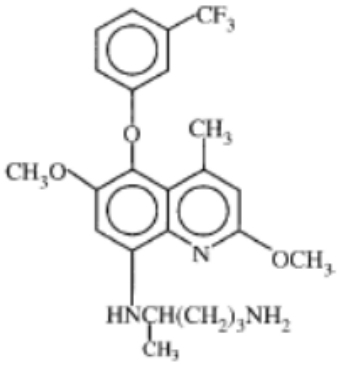
KODATEF™ was approved by the Australian Therapeutic Goods Administration in September 2018. Tafenoquine under the trade name KRINTAFEL also received approval from the US FDA for the radical cure (prevention of relapse) of *P. vivax* malaria in July 2018. The dosing regimen utilized in this study, 200 mg per day of tafenoquine for 3 days then weekly thereafter starting 7 days after the last loading dose is the same as that in the US FDA Prescribing Information.

Tafenoquine has been shown to be well tolerated and efficacious in the prevention of *Plasmodium* infections in nonclinical models and during Phase 1, 2 and 3 clinical studies in > 4,000 participants.

Figure 1: Structures of Primaquine and Tafenoquine



Primaquine



Tafenoquine

From (Brueckner 1998)

2.1.1. Ophthalmic Background

Ophthalmologic AEs reported during clinical trials of the tafenoquine Recommended Regimen are summarized in Table 1. Ophthalmologic AEs leading to study discontinuation were night blindness and reduced visual acuity, both of which affected the same participant (incidence 0.1%) in the tafenoquine Recommended Regimen group during a 6-month ophthalmic and renal safety study (Study 057). Keratopathy (corneal deposits) was reported as an SAE in 0.6% of participants in the tafenoquine Recommended Regimen group during the 6 month pivotal Phase III study in East Timor (Study 033, Nasveld 2010). The "keratopathy" (a term used by the initial reports) was presented in the analysis of the phospholipidosis safety subgroup as an SAE, as it was a significant new finding. These SAEs were subject to a 15-day Investigational New Drug (IND) safety report filed with the US FDA. No further cases of corneal deposits in Study 033 were reported as SAEs. Structurally, tafenoquine has cationic amphiphilic characteristics, and accordingly it has potential to cause phospholipid accumulation (60P IB). The corneal deposits were not associated with any effect on visual acuity and were fully resolved in all participants by 1 year (Nasveld 2010). In addition, the SAE of "retinal disorders" occurred in 0.2% of participants who received the tafenoquine Recommended Regimen, a slightly lower incidence than was seen in the mefloquine group (0.3%). Eye disorders that occurred at incidences ≥ 1% in the tafenoquine Recommended Regimen group were conjunctivitis and keratopathy (corneal deposits), of which only keratopathy (corneal deposits) occurred at a higher incidence (8.2%) than in the

placebo population (0%). An expert panel reviewed the findings in Study 033 and concluded that the "keratopathy" was in fact benign and reversible. Study 057 did not track corneal changes as "keratopathy" but as eye test abnormalities. Therefore, corneal changes were not captured in Study 057 as AEs. In this protocol, the term "corneal deposits" will be used in preference to "keratopathy".

Ocular tissue imaging by means of OCT has become essential for the evaluation of retinal diseases and treatment decisions (Wenner 2011). SD-OCT, also known as Fourier-domain OCT has resulted in improved resolution of the B-scan images (Grover 2009). These newer high-resolution instruments can show localized thinning of the retinal layers in the parafoveal region and confirm drug toxicity. Loss of the inner/outer segment line (now known as the ellipsoid zone) may be an early objective sign of parafoveal damage (Marmor 2016). Normal reference values for macular thickness have been previously established by Time Domain (TD) Stratus OCT and this study will use a normative range value of 222-318 μm for study participants (Appendix 4) using SD-OCT. TD-OCT is no longer recommended (Section 2.1.1.3). A literature search showed that macular thickness can be different between different racial or ethnic groups and can be further affected by age, gender, refractive error and axial length. It is important to note that changes in foveal thickness are expected to be found in eyes with symptomatic macular pathology (Wenner 2011). However, toxic maculopathy tends to start in the parafoveal region without acuity loss. Therefore, total macular volume and parafoveal (inner ring of ETDRS grid) thickness are also examined as one of the secondary endpoints in this study.

Table 1: Summary of Ophthalmologic AEs: Tafenoquine Recommended Regimen Group vs Placebo and Mefloquine

	Number (%) of Subjects		
	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (Recommended Regimen) (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
AEs leading to Discontinuation			
Metamorphopsia	0	1 (0.3%)	0
Night blindness	1 (0.1%)	0	0
Visual acuity reduced	1 (0.1%)	0	0
Ophthalmologic SAEs			
Keratopathy	5 (0.6%)	0	0
Retinal disorder	2 (0.2%)	0	1 (0.3%)
Metamorphopsia	0	1 (0.3%)	0

Table 1: Summary of Ophthalmologic AEs: Tafenoquine Recommended Regimen Group vs Placebo and Mefloquine (Continued)

	Number (%) of Subjects		
	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (Recommended Regimen) (n=825)	**Placebo (n=396)**	**Mefloquine 250 mg daily x 3 days, then 250 mg weekly (n=309)**
Ophthalmologic AEs Occurring in ≥1% of Study Subjects			
Conjunctivitis	24 (2.9%)	18 (4.5%)	13 (4.2%)
Keratopathy	68 (8.2%)[a]	0	0

[a] Reported as an AE only in a small cohort of Study 033 that was targeted for specialized eye tests (phospholipidosis safety subgroup). After the initial 5 cases were reported as SAEs (a significant new safety finding), the remainder of the keratopathy reports in the phospholipidosis safety subgroup were reported as AEs only.

2.1.1.1. Corneal Deposits

Corneal deposits are thought to be a manifestation of systemic phospholipidosis. This metabolic effect of tafenoquine was observed during 3-6 month repeat dose toxicity studies in mice, rats and dogs. In addition to corneal deposits, findings indicative of systemic phospholipidosis included foamy macrophage accumulation and lamellar inclusion bodies in alveolar macrophages and type II pneumocytes, and eosinophilic material in alveoli of the lung. Generally, these effects were similar between species and were both time- and dose-dependent. Phospholipidosis is a well-documented effect resulting from an accumulation of intracellular phospholipids, which is known to occur with cationic amphiphilic drugs such as tafenoquine and many other antimalarials (Halliwell 1997). The lesion is characterized by excessive accumulation of foamy alveolar macrophage, mononuclear cells and amorphous material in alveolar spaces (Halliwell 1997). This response is considered an adaptive response to the presence of the drug and is not necessarily a toxic response nor is it predictive of similar findings clinically. There appeared to be no linked functional consequence to the phospholipidosis effects in animals, except for one dog receiving 4.0 mg/kg/day in the 12-month study showing increased respiratory rate and the largest lung weight compared to control males. Foamy macrophages have also been reported following 2-years administration of chloroquine to rats (Nelson 1948) and the FDA review of phospholipidosis indicated that over 50 marketed and experimental drugs of a cationic amphiphilic structure from a wide variety of pharmacological classes induce this effect (Sadrieh 2010).

Signs of phospholipidosis in man were monitored for during Study 033. A subset of 95 participants was assessed for the possible effects/signs of phospholipidosis on the eye (ophthalmic assessments), lung function by measurement of the diffusion capacity of the lungs to carbon monoxide (indicator of disease) and forced expiratory volume (FEV_1), and by electron microscopy examination of white blood cells (WBCs) prior to and after 6 months' treatment. Of the phospholipidosis safety subgroup, 74 participants had been randomized to receive the tafenoquine Recommended Regimen.

No significant effects were noted for the lung or electron microscopy examination of WBCs. However, at the end of the study's prophylactic period (6-month visit), 69 (93.2%) of the

74 participants randomized to tafenoquine among the phospholipidosis safety subgroup had developed corneal deposits initially categorized as "keratopathy". There were no changes in tests of visual fields, visual acuity, or color vision in these participants. The majority of participants with corneal changes (42 of 69) had resolution at 3 months after the end of the prophylactic period, while the remainder had complete resolution of their 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, the aim of Study 057 was to provide further evidence of the ophthalmic safety of tafenoquine for its use as an antimalarial agent (Leary 2009). Although the corneal deposits observed in Study 033 had resulted in no evident effects on vision, their possible effect on night vision had not been evaluated. Since impairment of night vision would prevent active duty soldiers from fully performing their duties, the possibility of tafenoquine adversely affecting night vision was investigated in Study 057. The visual impact of corneal deposits was assessed using multiple tests, including measurement of forward light scatter (FLS), low contrast visual acuity (LCVA), mesopic contrast threshold (MCT), and scotopic contrast threshold (SCT). The primary ophthalmic safety endpoint was the number of participants with impaired night vision due to corneal deposits, as measured by the FLS test. Overall, there were no FLS test failures in either treatment group. The results of the primary ophthalmic safety analysis clearly showed that night vision was unimpaired in the tafenoquine-treated group. The secondary ophthalmic safety endpoints that assessed deterioration in night vision via LCVA, MCT, and SCT testing showed similar findings for tafenoquine Recommended Regimen participants and placebo participants. In summary, there was no evidence in Study 057 that exposure to tafenoquine had an adverse effect on the quality of vision.

In Study 057, 10 (14.3%) participants in the tafenoquine Recommended Regimen group and 7 (21.9%) participants in the placebo group had evidence of corneal deposits in either eye at screening. After the screening visit, 15 (21.4%) participants receiving tafenoquine and 4 (12.5%) participants receiving placebo developed new-onset corneal deposits in one or both eyes during the study. Approximately 60% of the corneal deposit cases among participants receiving tafenoquine and 100% of the cases among participants receiving placebo emerged by Week 12 of the study. No trends were apparent with respect to the time to onset of these new corneal deposits in participants who did not have corneal abnormalities at screening. New-onset corneal deposits in all four participants in the placebo group resolved within 6 weeks of onset, while in the tafenoquine Recommended Regimen group, corneal deposits resolved within 12 weeks of onset in all but one participant. Corneal deposits in the remaining tafenoquine-treated participant resolved by Week 48.

In summary, benign, reversible corneal deposits have been noted in some participants treated with the tafenoquine Recommended Regimen. Participants are unaware of the development of these corneal deposits; it does not impact vision, and resolves within 1 year in all cases.

2.1.1.2. Retinal Effects

Retinopathy and night vision decline may also be a manifestation of systemic phospholipidosis. As previously described, selected participants in Study 033 underwent more detailed ophthalmic assessments (phospholipidosis safety subgroup). These included fundoscopy, which was performed at baseline (before tafenoquine dosing) and at 6 month's post-prophylaxis in 69 participants in the tafenoquine Recommended Regimen group and

17 participants in the mefloquine group. Examiners who performed the fundoscopy were aware of the participants' corneal deposits (if present) and were therefore unblinded in that respect. Fundoscopic examinations revealed abnormalities (e.g., granularity/pigmentation of retinal pigment epithelium [RPE], hard drusen) in 27 of 69 (39.1%) tafenoquine Recommended Regimen participants and in 4 of 17 (23.5%) mefloquine participants at the end of dosing. Vision was not affected in any of these individuals. Among the participants 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 Recommended Regimen participants and in 1 of 1 (100%) mefloquine participants. When an expert ophthalmology board was asked to review this data, relevance of the retinal findings (based on fundoscopy and FFA) could not be ascertained because no baseline retinal photography data was available. The ophthalmology board noted that the results observed could reflect normal variability and the participative nature of the examinations. They did not consider that the FFA results provided evidence of a drug effect.

In Study 058, adult participants with confirmed *P. vivax* malaria received either tafenoquine 400 mg/day for 3 days (Days 1-3), or combination treatment with chloroquine and primaquine (chloroquine 100 mg on Days 1 and 2, chloroquine 500 mg on Day 3, and primaquine 15 mg on Days 3 through 16). Retinal safety assessments were performed at baseline (before dosing with IMP) and on Study Days 28 and Day 90. Retinal pigmentation was documented at the Day 28 assessment in 9 (19.6%) of patients with *P. vivax* malaria who received tafenoquine 400 mg/day x 3 days, and this pigmentation was still present in eight of the nine tafenoquine-treated malaria participants at Day 90. In comparison, 1 (4.2%) of the *P. vivax* participants who received chloroquine with primaquine developed retinal findings (described as mild mottling of the RPE or pigmentary changes). All of these AEs were mild and did not impact the vision of the participants. Of the nine retinal AEs reported at the Day 28 ophthalmic assessment, one had resolved by the Day 90 ophthalmic assessment and eight were reported as ongoing. These eight ongoing retinal AEs and the one first reported at the Day 90 assessment did not require further follow-up as they were all mild and did not affect the vision of the participants.

As in Study 033, the presence of retinal findings was not associated with any change in vision. An Independent Data Monitoring Committee (IDMC), which included two ophthalmic experts, reviewed all of the ophthalmologic safety data for all participants through the Day 28 assessment. Both ophthalmic experts concurred that there was no difference in visual function tests between the tafenoquine 400 mg group and the chloroquine with primaquine group. They also had no major concerns regarding findings in the digital photographs of the corneas or retinas, and they agreed that the eye findings did not raise undue concern, since visual function did not change. In addition, a blinded review of the retinal digital photographs conducted at the Fundus Photograph Reading Site, University of Wisconsin, found no evidence of anatomical changes consistent with retinal toxicity. The findings of the IDMC and blinded review of the digital retinal photographs were confirmed by an ophthalmology advisory board, which reviewed all of the ophthalmology safety data from the study and were in unanimous agreement that there was no evidence from the data presented of any impact on vision in participants taking tafenoquine. The IDMC also concluded that there was no evidence from assessment of the digital fundus images for any retinal toxicity.

During Study 057, retinal examinations were performed at baseline (before dosing with tafenoquine); during the 6-month dosing phase of the study (at 3 weeks, 6 weeks, 12 weeks,

18 weeks, and 24 weeks); and at the follow-up safety visit (at 12 weeks after tafenoquine dosing was completed). Retinal changes and impact on macular function were documented at each time point for each eye of every participant. Macular function tests included Amsler Grid, Humphrey Perimetry Test, high contrast visual acuity (HCVA), and color vision "color assessment and diagnosis" (CAD) test. There was no evidence that exposure to tafenoquine had any adverse effect on the retina. Assessment of macular function via the Amsler Grid Test, demonstrated no abnormalities in either eye for any participant in the tafenoquine group. Sporadic abnormalities across both treatment groups with the Humphrey Perimetry Test revealed no trends with respect to study treatment. Failures with the HCVA test were more frequent among tafenoquine participants at the Week 6 and Week 12 time points; however, at Follow-up (Week 12 and Week 24 after cessation of treatment), the incidence of failures was higher in the placebo group. A retinal abnormality (described as an area of retinal pigmentation that was not near the fovea) was identified by digital photography in the right eye of one participant (1.8% of the population) who received the tafenoquine Recommended Regimen. In that participant, the retinal changes were seen only at the follow-up visit. There were no retinal abnormalities in any participant in the tafenoquine Recommended Regimen group during the dosing phase of the study. In the placebo group, one participant (3.7% of the population) also had a retinal abnormality, which was similarly detected at the Follow-up visit. This study confirmed that administration of the tafenoquine Recommended Regimen for 6 months did not cause retinal toxicity in healthy participants.

2.1.1.3. Effects of Chloroquine/Hydroxychloroquine on the Retina

The exact mechanism of chloroquine (CQ) and hydroxychloroquine (HCQ) toxicity is not well understood. The classic clinical picture of a bilateral bull's-eye maculopathy caused by a ring of parafoveal RPE depigmentation that spares a foveal island should no longer be seen because screening tests will detect HCQ toxicity long before RPE damage is visible by imaging or fundus examination (Marmor 2016). In addition to being cationic amphiphilic drugs and thereby sharing potential issues of general toxicity concern with other phospholipidosis causing drugs (Nonoyama 2008), it is known that the highest concentrations of CQ and HCQ are found in melanin-containing tissues of the choroid and ciliary body of the eye (Mackenzie 1983) and that this binding to melanin in the RPE may serve to concentrate the drugs and contribute to, or prolong, their toxic effects (Marmor 2016). In practice the primary damage is to the photoreceptors, and as the outer nuclear layer degenerates, there is secondary disruption of the RPE. Additionally, CQ and less frequently HCQ can cause whorl-like intraepithelial deposits in the cornea. These are not associated with visual loss, and in contrast to retinopathy are usually reversible (Marmor 2016).

The most critical risk factor for the development of CQ or HCQ toxicity is excessive daily dose by weight of >5 mg/kg which dramatically increases both population risk and annual incremental risk (Marmor 2016). Duration of use is also linked to dosage as a critical factor. Some other preexisting medical conditions such as renal disease, tamoxifen use, and other retinal or macular diseases increase the risk further still. SD-OCT has become the recommended primary screening tool because it is objective, highly specific, and generally sensitive for levels of damage and thinning of the outer nuclear layer that might be visually significant (Marmor 2016).

2.1.2. Psychiatric and Neurologic Effects

Psychiatric AEs reported during clinical trials of the tafenoquine Recommended Regimen are summarized in Table 2. Psychiatric AEs leading to study discontinuation in the tafenoquine

Recommended Regimen group included depression and a suicide attempt, each of which occurred in one (0.1%) participant as follows:

- In Study 043, Subject 1166 (a 24-year-old Kenyan male) was withdrawn due to the SAE of alcohol intoxication/intentional self-injury (coded as a "suicide attempt") that occurred on Study Day 7 (total of 3 loading doses and 1 weekly dose of tafenoquine 200 mg). While acutely intoxicated with ethanol, the participant's self-destructive actions ("taking poison") had been reportedly prompted by marital problems. Subject 1166 was hospitalized, tafenoquine was discontinued, and the SAE was considered resolved in two days. The suicide attempt was considered to be a "severe" AE, which was "not related" to tafenoquine.
- In Study 033, Subject 26048, a 28-year-old white Australian Defence Force (ADF) soldier with a history of intracranial head injury, reported moderate depression beginning on Study Day 24. He was withdrawn from the study and treated with paroxetine, and his depression resolved after 87 days. The participant's depression was considered "suspected" related to tafenoquine.

In comparison, there were no psychiatric discontinuations in the placebo group, while in the mefloquine group; one participant was discontinued due to anxiety.

Insomnia as a psychiatric AE occurred at an incidence ≥1.2 % in the tafenoquine Recommended Regimen group (Table 2). In comparison, less than 1% of participants experienced insomnia in the placebo and mefloquine groups.

Because the comparator drug mefloquine carried a risk for psychiatric side effects (Barrett 1996; Croft 1996; Hennequin 1994; Lench 1995; Shlagenhauf 2003), the AE profile of tafenoquine was examined in greater depth for relatively rare AEs that occurred at extremely low incidences <1% (Table 2). Overall, participants in the tafenoquine Recommended Regimen group and the mefloquine group had comparable incidences of these rare psychiatric AEs, but both of these groups had higher incidences of psychiatric AEs than did placebo participants. Psychiatric AEs that occurred in tafenoquine Recommended Regimen participants 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. Of these, the majority affected only 1 to 2 participants each of the 825 participants in this group.

Five psychiatric AEs were observed in both the tafenoquine Recommended Regimen group and in the mefloquine group: insomnia, abnormal dreams, sleep disorder, nightmare, and depression. The incidences of these AEs were comparable between the two groups with the exception of insomnia, which occurred in a higher percentage of participants in the tafenoquine Recommended Regimen group (1.2%) than in the mefloquine group (0.3%).

Notably, both the tafenoquine Recommended Regimen group and the mefloquine group included military populations exposed to war-like conditions in Study 033, which is likely to have increased their risk for psychiatric AEs compared to participants taking placebo in a non-war like environment (Novitt-Moreno 2017).

A sub analysis of the AEs in the tafenoquine Recommended Regimen population (n=825) for the Integrated Safety Summary (ISS), showed that the percentage of AEs was markedly higher in the deployed ADF subgroup (n=492) (94.9%) compared with non-ADF participants (n=333) (67.6%). In addition, a much higher percentage of AEs in the ADF participants were

considered to be "not related" to treatment (86.7%) than in the non-ADF subgroup (53.0%). This suggests that the ADF subgroup had been exposed to extrinsic factors associated with their deployment in a hostile environment that influenced the safety findings in Study 033. Compared to non-ADF participants, deployed ADF participants had higher incidences of ear and labyrinth disorders, eye disorders, gastrointestinal (GI) disorders, immune system disorders, infections and infestations, injuries, poisonings, and procedural complications, musculoskeletal and connective tissue disorders, psychiatric disorders and skin and subcutaneous tissue disorders associated with military operations (Figure 2a). Conversely, non-ADF participants taking the tafenoquine Recommended Regimen had higher incidences of general disorders and administration site conditions, hepatobiliary disorders, investigation AEs, metabolism and nutrition disorders, nervous system disorders, renal and urinary disorders, reproductive system and breast disorders, and respiratory, thoracic, and mediastinal disorders (Figure 2b) consistent with a more mundane home-centered lifestyle with its associated risk of typical nasopharyngeal infections, coughs, constipation, and headaches. In some cases, (primarily in African studies) there was also a risk for endemic concurrent infections (e.g., amebiasis and helminthic infections) and for suboptimal nutrition.

Notably, for many of the AE categories, the profile of the non-ADF subgroup on tafenoquine was similar to that of placebo (n=295). This included ear and labyrinth disorders, eye disorders, GI disorders, infections and infestations, investigation AEs, musculoskeletal and connective tissue disorders, nervous system disorders, reproductive system and breast disorders, and skin and subcutaneous tissue disorders (Figure 2c).

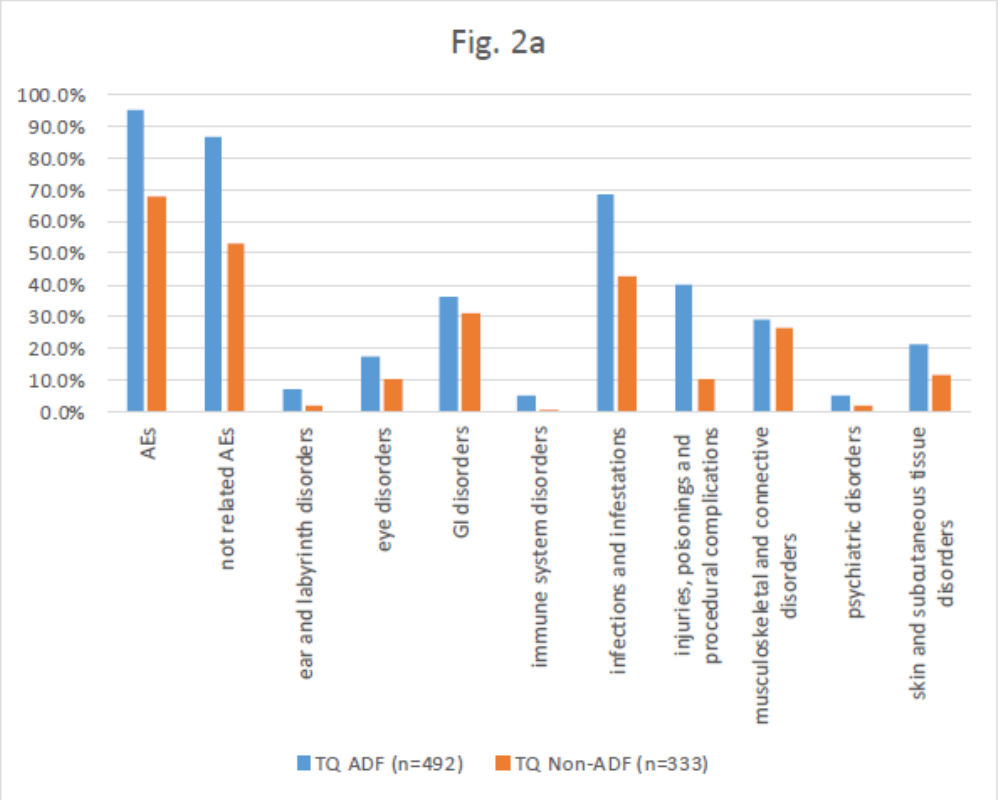
To examine further, whether specific extrinsic factors could be identified in participants who reported psychiatric AEs in the ADF subgroup versus the non-ADF subgroup, medical histories and non-psychiatric AEs were reviewed for participants who reported insomnia or sleep disorder in these two subgroups. Concurrent GI illnesses, active pain, or upper respiratory illnesses affected eight out of 10 participants with insomnia or sleep disorders in the ADF subgroup and two of three participants in the non-ADF subgroup. When these confounding illnesses and events were eliminated, comparable percentages (0.3%-0.4%) of the two subgroups experienced insomnia or sleep disorders. In terms of the tafenoquine Recommended Regimen overall population, although insomnia (1.2%) or sleep disorder (0.4%) was reported in 1.6% of this population, only 3 of 825 participants (0.4% of the tafenoquine Recommended Regimen overall population) did not have an identifiable concurrent illness or injury that might have contributed to their insomnia or other reported sleep disorders. The LSEQ will be used to measure difficulty of getting to sleep, quality of sleep, awakening, and participants behavior following wakening (Appendix 4). The DHI will be added to assess dizziness and vertigo severity with respect to normal functioning if this AE is reported (Appendix 5). Although the suicide attempt of a subject in Study 043 was considered unrelated to tafenoquine, the C-SSRS interview will be used in this study to document subjects' suicidal ideation or any suicide attempt.

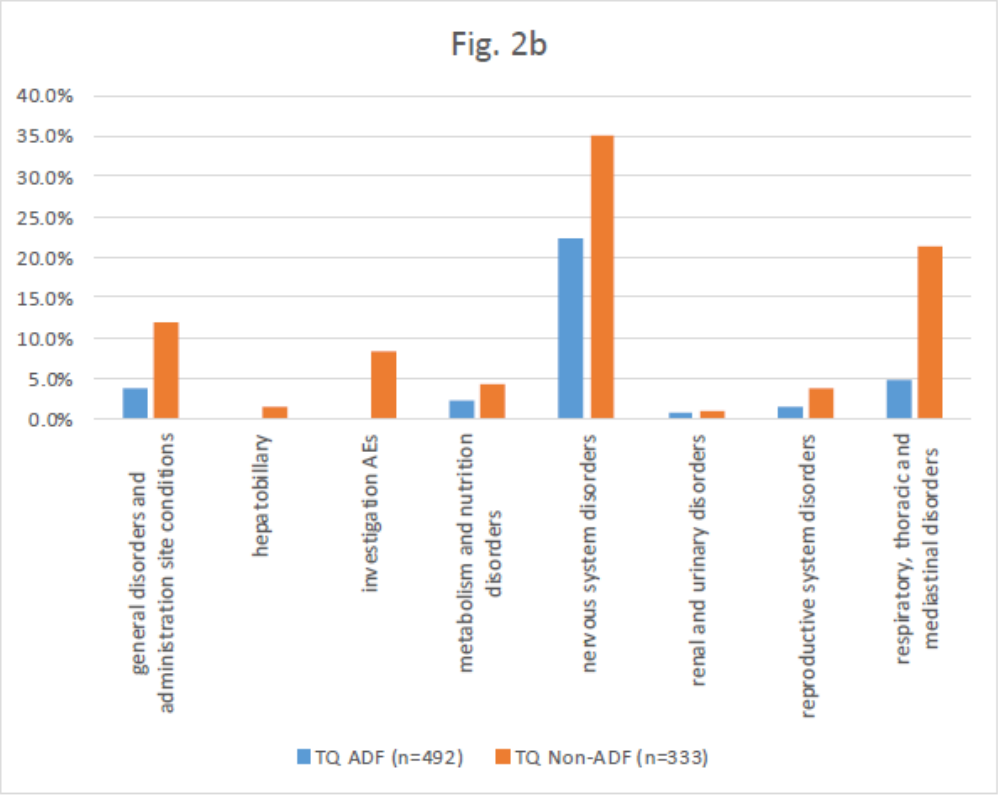
Table 2: Summary of Psychiatric Adverse Events: Tafenoquine Recommended Regimen Group vs Placebo and Mefloquine

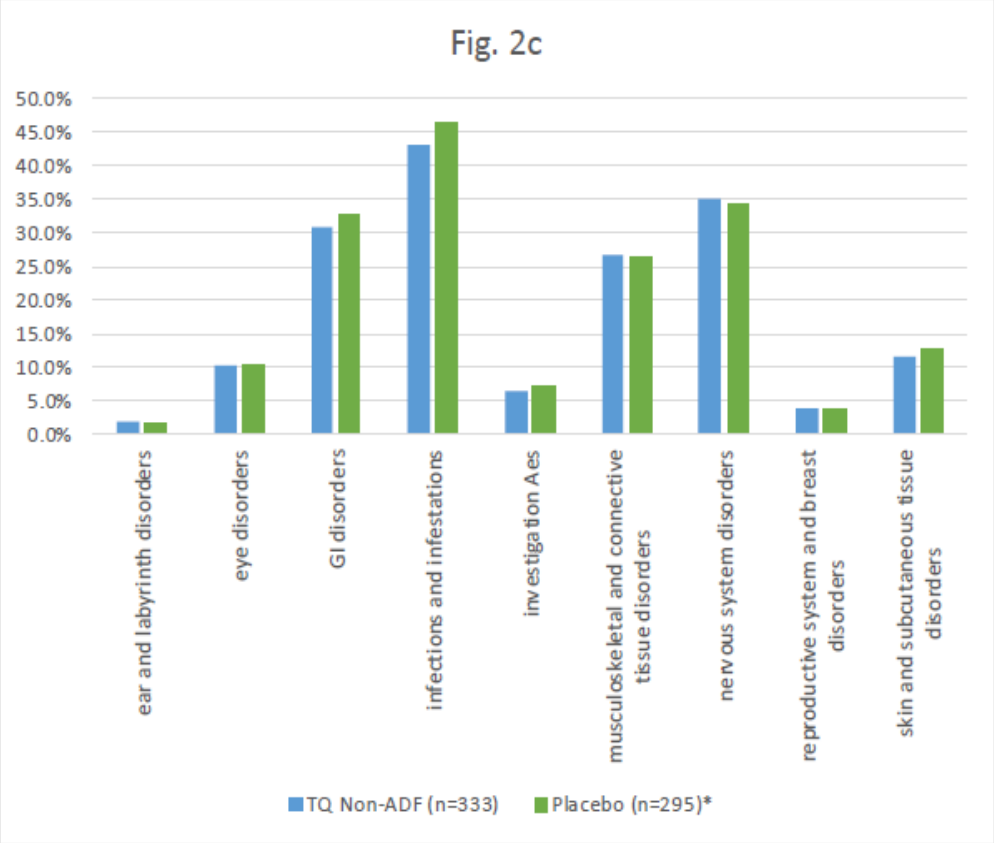
	Number (%) of Subjects		
	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (Recommended Regimen) (n=825)	**Placebo (n=396)**	**Mefloquine 250 mg daily x 3 days, then 250 mg weekly (n=309)**
Included Studies	030, 033, 043, 045, 057	030, 043, 044, 045, 057	030, 033, 045
AEs leading to Discontinuation			
Anxiety	0	0	1 (0.3%)
Depression	1 (0.1%)	0	0
Suicide attempt	1 (0.1%)	0	0
Psychiatric SAEs			
Anxiety	0	0	1 (0.3%)[a]
Suicide attempt	1 (0.1%)[a]	0	0
AEs Occurring in ≥1% of Study Subjects			
Insomnia	10 (1.2%)	3 (0.8%)	1(0.3%)
AEs Occurring in ≤1% of Study Subjects			
Abnormal dreams	5 (0.6%)	0	2 (0.6%)
Sleep disorder	3 (0.4%)	0	2 (0.6%)
Nightmare	3 (0.4%)	0	1 (0.3%)
Depression	2 (0.2%)	0	1 (0.3%)
Agitation	2 (0.2%)	0	0
Anxiety Disorder	2 (0.2%)	0	2 (0.6%)
Euphoric mood	2 (0.2%)	0	0
Bipolar disorder	1(0.1%)	0	0
Depressed mood	1(0.1%)	0	0
Neurosis	1(0.1%)	0	0
Panic attack	1(0.1%)	0	0
Stress	1(0.1%)	0	0
Suicide attempt	1(0.1%)	0	0
Somnambulism	0	0	1 (0.3%)
Loss of libido	0	0	1 (0.3%)

[a] SAE led to discontinuation

Figure 2: Subjects with Specific Categories of Adverse Events. Tafenoquine Recommended Regimen groups in ADF population versus non-ADF population versus placebo







2.2. Nonclinical Studies

2.2.1. Nonclinical Pharmacology

The intrinsic prophylactic effect of tafenoquine has been evaluated against various patient isolates and parasite clones *in vitro* from diverse geographic regions where *P. falciparum* is prevalent. Tafenoquine was proven more active than primaquine against *P. falciparum* isolates from Gabon (Central Africa), Senegal (West Africa), and Djibouti (East Africa) (Pradines 2006). In sponsor's studies, tafenoquine was 1.3- to 18-fold more active than primaquine on an equimolar basis *in vitro*. Furthermore, there are no obvious patterns of cross-resistance between tafenoquine and other antimalarial drugs (Vennerstrom 1999).

Multi-drug resistant strains of *P falciparum* were susceptible to tafenoquine *in vitro* (Ramharter 2002). Tafenoquine exhibited equivalent activity to primaquine against chloroquine-susceptible strains; however, chloroquine-resistant and other multi-drug (mefloquine, pyrimethamine) resistant parasite strains were more susceptible to tafenoquine. *In vivo*, tafenoquine demonstrated curative and prophylactic effects in mice and monkeys following subcutaneous and/or oral administration. In primate models, blood stages of chloroquine-resistant *P. vivax* were successfully treated with tafenoquine. Tafenoquine also showed blood schizonticidal activity against two simian malaria infections, *P. cynomolgi bastianelli* and *P. fragile*, in rhesus monkeys (Puri 2003).

Unlike blood schizonticides such as mefloquine, which are only active against asexual blood forms, 8-aminoquiniolines such as tafenoquine and primaquine are effective against both initial liver forms and subsequent blood asexual forms. Prophylactic activity against the initial liver or blood forms are termed "causal" or "suppressive" activity, respectively, since

liver activity treats the underlying "cause" of subsequent blood infection and blood activity "suppresses" parasites that emerge from the liver but does not attack the cause. It is difficult to precisely determine the ratio of causal activity to suppressive activity for the 8-aminoquiniolines, since this determination requires separate quantification of parasite elimination in the liver versus elimination in the blood. This experiment has only been performed once, in the luciferase-tagged *P. berghei* infected mouse model (Li 2014).

Because this parasite is luciferase-tagged, parasite luminescence in the liver can be measured separately from luminescence of the rest of the body. In the *P. berghei* infected mouse, parasites emerge from the liver to infect the blood at 48 hours (2 days) after sporozoite challenge, and tafenoquine has a $t_{½}$ in the blood of 66 hours (3 days). After a single dose of 5 mg/kg tafenoquine on Day (-1), the day prior to sporozoite dosing, 10 of 10 (100%) tafenoquine-treated animals were protected. Elimination of liver parasites was not quite complete (98.6% were eliminated) at 48 hours. Since 100% of parasites were eliminated at 72 hours, 1.4% of parasites escaped being killed in the liver but were then killed in the blood by tafenoquine that is present three days after dosing (Li 2014).

In a causal prophylactic experiment, rhesus monkeys were dosed orally with 0.1, 0.316, 1.0 or 1.78 mg/kg/day of tafenoquine for three days. A later phase of the experiment dosed monkeys orally at lower doses of 0.0316, 0.1 or 0.316 mg/kg/day for 3 days to validate results seen in the initial phase. Monkeys were dosed with *P. cynomolgi* sporozoites on Day 0. A vehicle control and a positive control (primaquine) were dosed in each group of inoculated monkeys. Blood smears were examined from Day 7 to 70 to observe patency. Tafenoquine doses of 0.316, 1 or 1.78 mg/kg/day given orally for three days were found to be protective in all monkeys dosed while one of two monkeys dosed at 0.1 mg/kg/day became patent (showed infection). These data were further validated at doses of 0.0316, 0.1 and 0.316 mg/kg/day given orally for three days where doses of 0.316 mg/kg/day was protective in 5 out of 5 (100%) of monkeys while the lower doses were ineffective. The calculated effective dose to eradicate 50% of the target pathogen (ED_{50}) for tafenoquine was 0.124 mg/kg for 3 days. In this study, it was concluded that tafenoquine was effective at preventing sporozoite induced infections of *P. cynomolgi* when oral doses of ≥0.3 mg/kg/day were given for 3 days. The calculated causal prophylactic ED_{50} was 0.124 mg/kg/day for 3 days. This represents activity 10.5 times more potent than primaquine against pre-erythrocytic stages of *P. cynomolgi* (Milhous 1998). A single dose of 5.68 mg/kg tafenoquine was fully protective when given 3 days prior to challenge. A dose of 5.34 mg/kg primaquine was protective when administered on the day of infection (DiTusa 2014, Milhous 1998).

In a test designed to evaluate the tissue schizonticidal (radical curative) activity of tafenoquine in Indian rhesus monkeys infected with *P. cynomolgi* sporozoites, following infection, tafenoquine dosing (0.0316, 0.1, 0.3161 and 1.0 mg/kg/day) was given once a day for 7 consecutive days after parasite count exceeded 5000/mm^3 and following a completely suppressive blood schizonticidal regimen of chloroquine. It was concluded that tafenoquine given orally for seven days at doses ≥0.1 mg/kg/day in combination with chloroquine (3.1 mg/kg/day) was effective in curing an established tissue infection of *P. cynomolgi* in rhesus monkeys. The calculated 50% curative dose (CD_{50}) for tafenoquine was 0.172 mg/kg/day given over seven days making it 7.4 times more active than primaquine (Study SEATO 338).

Similarly, the total minimum curative dose of tafenoquine monotherapy for radical cure of *P. cynomolgi bastianelli* infected Indian rhesus monkeys (*Macaca mulatta*) is 18 mg/kg (6 mg/kg/day over three days) and the minimum total dose required to clear blood stage

parasites is 6 mg/kg (2 mg/kg/day over three days). In this relapsing malaria model, animals were infected with 1 million sporozoites intravenously (IV) and microscopy was conducted daily from Days 6-21 post-inoculation until the animals became patent (Day 8). Tafenoquine was administered once the parasitemia reached 5000/µL resulting in cure within 3.5 days. The minimum blood stage clearance dose (2 mg/kg/day) in Indian rhesus monkeys is equivalent to a dose of 38.7 mg/kg/day in humans (271 mg total dose) based on standard bodyweight conversion and a human body weight of 60 kg (FDA 2005). At this curative dose, parasitemia continued to rise in the Indian rhesus monkeys from Day -1 to Day 1 before rapidly declining from Day 2-3 (Dow 2011).

In the *in vitro* human ether-a-go-go related gene (hERG) channel electrophysiology assay, the 50% maximal inhibitory concentration (IC_{50}) value for inhibition of hERG tail current was 1.1 µM (equivalent to 0.510 µg/mL), a relatively low micromolar value and approximately equivalent to the predicted plasma concentration at the maximum proposed dose in humans. However, there were no adverse effects observed in the ECG evaluations (including QTc interval) conducted in *in vivo* oral and IV cardiovascular and pulmonary safety pharmacology studies in dogs, and in repeat dose oral toxicity studies in dogs of up to 52 weeks in duration, in which plasma tafenoquine concentrations of ~18.4 µg/mL and greater were achieved. In addition, there were no remarkable effects on action potential parameters in an *in vitro* dog isolated Purkinje fiber assay at concentrations up to 10 µM. Therefore, tafenoquine has a low potential for QTc prolongation, which is supported by thorough QT/QTc clinical investigations (Green 2014).

2.2.2. Pharmacokinetics and Product Metabolism in Animals

In nonclinical species, the absorption of tafenoquine appeared to be slow (highest plasma concentrations generally >3 hours after dosing) and was incomplete in rats, but high in dogs, with a long elimination $t_{1/2}$ (40 hours or greater). In the primary toxicology species (rat and dog) systemic exposure increased proportionally with dose and there was substantial accumulation of tafenoquine following repeat oral administration, consistent with its long half-life. No sex differences in systemic exposure were observed in the mouse, rat or dog (Study 6, Study SBF/232, Study 8740-87-5 and Study 802/589).

In vitro, plasma protein binding in the mouse, rat, dog and human was very high (≥99.5%) (Study DI00292 and Study DI99078). Tafenoquine association with blood cells was 77%, 54% and 57%, in rat, dog and human, respectively. Incubation with rat, dog and human plasma in the light resulted in irreversible binding of some tafenoquine-related material to plasma protein (22% to 34%, compared with 1% for samples stored in the dark), and light-induced degradation of tafenoquine to a quinoneimine structure was postulated as a possible mechanism.

Following a single oral dose of [^{14}C]tafenoquine to rats, radioactivity was widely distributed by two hours post dose and most tissues contained concentrations of radioactivity greater than those in blood with the exception of the brain and the spinal cord (Study SB-252263/RSD-101HHL/1). Tissue concentrations of radioactivity declined slowly with time and at 10 days after dosing, most tissues still contained quantifiable amounts of radioactivity. This was consistent with slow elimination of radioactivity from intact and bile duct cannulated (BDC) rats and dogs, which occurred primarily via the bile/feces (accounting for ~75% and 40% of the dose in rats and dogs, respectively). Fecal elimination also predominated in intact monkeys (~56% of the dose) (Study 9).

In rats, dogs and humans, the only notable drug-related material detected in the plasma was unchanged parent compound. The primary metabolites detected in rat and/or dog bile included the products of O-demethylation; oxidation to alcohols, ketones and carboxylic acids; deamination and N-dealkylation. Desaryl metabolites were present as imino/keto and di-imino compounds or tautomers of these structures. Tafenoquine was the major identifiable component of fecal extracts from both intact and BDC rats and dogs (Study DI99224). In humans, metabolites detected in the urine were largely those previously seen in rats and/or dogs.

Despite tafenoquine inhibiting a variety of cytochrome P450 (CYP) enzymes *in vitro* (including CYP1A2, 2C9, 2D6 and 3A4/5) (Study 040), subsequent clinical studies have shown a low risk of meaningful drug-drug interactions via these enzymes. Furthermore, tafenoquine did not activate the human pregnane-X-receptor (PXR), using an *in vitro* reporter gene assay, suggesting that tafenoquine is unlikely to perpetrate a drug-drug interaction as a result of induction of CYP3A4 (60P IB).

Tafenoquine inhibited the *in vitro* transport of [^{14}C] metformin via human organic cation transporter 2 (OCT2), multidrug and toxin extrusion 1 transporter (MATE1), and multidrug and toxin extrusion 2K transporter (MATE-2K) with calculated IC_{50} values of 0.28, 2.0 and 0.63 µM, respectively. Based on unbound systemic concentrations at therapeutic doses, and the IC_{50} derived, there is a potential, but low risk of drug interactions with OCT/MATE substrates (60P IB).

2.2.3. Nonclinical Toxicology

The key target tissue effects in repeat dose toxicology studies of tafenoquine of up to 26 and 52 weeks duration in rats and dogs, respectively, were oxidative changes in red cell elements of blood (methemoglobinemia, Heinz bodies, decreased hemoglobin concentration) and findings indicative of phospholipidosis (foamy macrophage accumulation, lamellar inclusion bodies in alveolar macrophages and type II pneumocytes, and eosinophilic material in alveoli), which were manifested principally in the lung. Hemosiderin deposition in various tissues, increased spleen weight and bone marrow hyperplasia were associated with the RBC effects. A renal tubular lesion in mice and rats may have been a consequence of hemoglobin reabsorption and breakdown. There were no significant renal changes observed in the dog, with only slight pigment deposition noted. Hepatic findings (including increased weight, small increases in plasma enzyme markers, subacute inflammation and fatty changes) may reflect pathophysiological responses to either or both anemia or altered phospholipid accumulation. All of the principal pathological changes were fully reversible, or showed partial reversibility, following a 13-week drug-free recovery period in the 13-week studies.

Based on the phospholipidosis-related changes in the lungs, the approximate overall no effect dose was 0.5 mg/kg/day (26 weeks) in rats and 0.1 mg/kg/day (52 weeks) in dogs. Findings increased in severity with both dose and duration of tafenoquine administration, thereby reducing the no effect dose to lower doses in the repeat dose toxicity studies conducted for shorter periods of time than 26 weeks in rats and 52 weeks in dogs. In separate 8-week toxicokinetic studies using the same doses as the repeat dose studies, the no effect dose was shown to be associated with plasma area under the concentration-time curve from 0 to one week ($AUC_{0\text{-}1}$ week) values of 6.66 µg·h/mL in rats and 6.84 µg·h/mL in dogs (sexes combined).

No ophthalmological changes have been observed in any of the nonclinical animal toxicity studies.

In a neurobehavioral, histopathologic and toxicokinetic study performed using single super-therapeutic doses of tafenoquine (125, 250 or 500 mg/kg) in rats, tafenoquine appeared to be free of neurologic toxicity (Dow 2017). There were no drug-related findings in the brain sections of rats dosed with 500 mg/kg tafenoquine (the minimum lethal dose) compared to controls. There was no evidence of neurodegeneration or other morphological abnormalities; axon morphology was comparable between tafenoquine-treated and control animals; and the gracile nucleus, thought to be a potential target for toxicity, showed no abnormalities.

No adverse effects on fertility or embryofetal development (including at maternally toxic doses), or on post-natal survival, were observed in a complete battery of developmental and reproductive toxicology studies as well as a juvenile toxicity study.

Standard *in vitro* and *in vivo* genotoxicity studies for tafenoquine led to the conclusion that tafenoquine itself does not present a genotoxic risk to humans.

When compared to the area under the curve (AUC) in humans consequent to the Recommended Regimen of tafenoquine (200 mg x 3 days followed by 200 mg/week), systemic exposures at the no effect doses in both rat and dog were assessed as representing relatively small fractions (~12%) of the AUC in humans, further confirming the observed heightened sensitivity of the two animal species to the treatment-related phospholipidosis and hematological effects seen with tafenoquine (60P IB).

2.3. Clinical Studies

The clinical development program for tafenoquine has spanned decades and consists of 16 Phase 1, nine Phase 2 and two Phase 3 clinical studies in more than 4,000 participants. The studies have included single and multiple oral dose studies, single dose rising studies in fasted and non-fasted participants, bioavailability studies for different tafenoquine formulations, drug-interaction and safety studies and malaria challenge studies. Field studies to assess tafenoquine efficacy have been conducted in Africa and Asia (60P IB).

2.3.1. Efficacy

Phase 1 malaria challenge studies and Phase 2 and 3 clinical studies with tafenoquine have shown the potential utility of tafenoquine in the chemoprophylaxis of *P. falciparum* and *P. vivax* malaria (reflecting activity against initial liver forms and blood asexual forms) and in the radical cure/relapse prevention in *P. vivax* infection (reflecting activity against liver hypnozoites). Tafenoquine also has anti-gametocidal activity (Study 058).

Tafenoquine has been assessed for its ability to treat existing infection with *P. vivax*. Parasitemia (parasites/µL) was recorded on Day 0 (the day treatment was started) as well as on Days 1 and 2 after treatment was started. In 43 patients, mean (highest) parasitemia values were: 8000 (44000) and 8000 (49000) for AM and PM on Day 0; 6000 (2000) and 5000 (16000) for AM and PM on Day 1; 3000 (12000) and 2000 (10000) for AM and PM on Day 2. For a randomized group of 22 patients administered standard therapy with chloroquine/primaquine, values were: 6000 (30000) and 8000 (40000) for AM and PM on Day 0; 2000 (4000) and 1000 (12000) for AM and PM on Day 1; 100 (500) and 100 (100) for AM and PM on Day 2. These data indicate that for treatment of *P. vivax*, the decline of parasitemia with time is slower for tafenoquine than for a standard blood schizonticide such as chloroquine, but this observation is of little consequence for chemoprophylactic use of the drug as a monotherapy (Study 058).

Pivotal trials in Oceania and in Africa have shown tafenoquine to have the same prophylactic efficacy as mefloquine. For non-immunes in Oceania where the incidence of *P. falciparum* and *P. vivax* malaria in non-chemoprophylaxed persons was estimated to be 1% and 7% respectively, the prophylactic efficacies of weekly tafenoquine and mefloquine were both 100% (Dow 2014). For semi-immunes in Africa where the incidence of *P. falciparum* infection in placebos was measured as 32%; the number of persons infected in the weekly tafenoquine and mefloquine groups were each 2% (Dow 2015).

2.3.2. Human Safety Data

Tafenoquine has been evaluated in over 4,000 healthy volunteers and patients with malaria in Phase 1, Phase 2, and Phase 3 clinical studies including single and multiple oral dose studies, dose rising studies in fasted and non-fasted participants, bioavailability studies for different tafenoquine formulations, drug-interaction studies, malaria challenge studies, malaria prophylaxis and *P. vivax* malaria treatment studies. In the studies conducted to date, a capsule formulation containing dosage strengths of 4 mg, 14 mg, 25 mg, 50 mg, 100 mg, 200 mg and 250 mg of tafenoquine (as tafenoquine succinate) was studied. Undesirable effects in this large sample of participants and patients administered multiple doses can be summarized as the following and are presented in Table 3:

- Blood and lymphatic system disorders, including hemolytic anemia (in patients with G6PD deficiency) and methemoglobinemia.
- Corneal deposits that are fully reversible (within 1 year). Notably, no treatment-related retinal findings were observed following extended treatment (200 mg x 3 days loading dose followed by 200 mg/week for 23 weeks) in a Phase 1 clinical safety study (Leary 2009; Study 057).
- GI disorders: nausea, vomiting, abdominal pain and diarrhea.
- Immune system disorders: hypersensitivity reactions including urticaria.

Table 3: 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	All Tafenoquine Subjects (N=825)	Non-Deployed Tafenoquine Subjects (N=333)	Placebo (N=396)
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%)
Diarrhea	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%)

Table 3: Adverse Events occurring in ≥1% of Subjects in the Tafenoquine ACR Group and with an Incidence Numerically Greater than in the Placebo Group (Continued)

Adverse Reaction	All Tafenoquine Subjects (N=825)	Non-Deployed Tafenoquine Subjects (N=333)	Placebo (N=396)
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
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%)
GERD	14 (1.7%)	1 (0.3%)	1 (0.3%)
Arthropod bite	14 (1.7%)	2 (0.6%)	2 (0.5%)
Ingrowing nail	12 (1.5%)	0	0
Ear pain	11 (1.3%)	5 (1.5%)	4 (1.0%)
Otitis externa	11 (1.3%)	2 (0.6%)	4 (1.0%)
Heat illness	11 (1.3%)	0	0
Ligament sprain	10 (1.2%)	4 (1.2%)	0
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

*Early reports of corneal deposits thought to be secondary to phospholipidosis were initially reported as keratopathy and reported as SAEs. Once these were determined to be benign and reversible, later reports of keratopathy were not reported as SAEs.

2.3.3. Human Pharmacokinetic Data

In PK studies in humans, AUC and maximum concentration (C_{max}) of tafenoquine increased in a dose proportional fashion, and the mean terminal half-life ($t_{1/2}$) of tafenoquine ranged from 13 to 15 days. Food can increase the absorption of tafenoquine, as AUC and C_{max} increased 41% and 31%, respectively, when the drug was administered with a high fat meal

compared with dosing in the fasted state. However, tafenoquine can be taken with or without food at the recommended dose to produce therapeutic blood levels, so there are no dietary restrictions.

Population PK analysis showed that tafenoquine typical values of the first-order absorption rate constant (ka), clearance (CL/f) and volume of distribution (V/f) were 0.243 h^{-1}, 0.056 L/h/kg and 23.7 L/kg, respectively, and the mean elimination $t_{½}$ was 12.7 days. Only body weight had a significant effect on V/f and CL/f, both increasing with increasing weight (60P IB).

3. STUDY RATIONALE

Previous studies in over 4,000 healthy volunteers and patients suggests tafenoquine is safe and efficacious when given over a period of 6 months.

This study will evaluate the overall safety and tolerability of tafenoquine for long-term use (12-months). Participation in the study will be approximately 80 weeks, including a screening period of up to 4 weeks, a 52 week dosing period (including the loading dose in Week 1), and a 24-week follow-up period.

This study aims to expand the safety database for tafenoquine for a 12-month period of exposure by examining general tolerance and detailed assessments of ophthalmologic parameters, clinical laboratory tests, and psychiatric evaluation to support the use of tafenoquine as a potential antimalarial prophylactic drug to prevent malaria in adults for longer term use. Specifically, ophthalmologic changes will be assessed from Screening using SD-OCT (including wide field macular scan) and qFAF at Weeks 12, 24, 52, and 64 (Visits 4, 5, 6, and 7), and if required also at Weeks 76, 89 and 104 (Visits 8, 9 and 10) in healthy (G6PD normal) adult participants, dosed with tafenoquine 200 mg once a day (QD) for 3 days and then 200 mg every week up to 51 weeks. Additional ophthalmic assessments will include BCVA using the ETDRS chart, FM-100 hue test, Mars letter contrast sensitivity test, M-chart, slit lamp evaluations of the corneal epithelium, microperimetry and retinal digital photography (conventional and wide field, to enable detection of subtle peripheral toxicity). The incidence, severity and relationship to tafenoquine of AEs (unexpected toxicities, AEs encountered during or after tafenoquine administration), safety laboratory parameters, and vital signs and ECG up to and including Week 64 (Visit 7) at a ≥ 1% (common) or ≥10% very common frequency. A placebo control group will be used to compare the results in the tafenoquine group.

While neurologic and psychiatric events are rare, neurologic and psychiatric AEs have been reported in clinical trials conducted with tafenoquine and mefloquine. The AEs reported in the treatment group were: abnormal dreams, sleep disorders, nightmares, depression, agitation, anxiety disorder, euphoric mood, bipolar disorder, depressed mood, neurosis, panic attack, stress, and suicide attempt.

This study will continue the characterization of the exposure-response relationship for these AEs including sleep disturbances assessed using the LSEQ and the development of psychiatric disorders in accordance with DSM-5 criteria using the M.I.N.I. English Version 7.0.2 and suicidality using the C-SSRS. The DHI will be used to assess severity of dizziness as it relates particularly to effects on functioning, if dizziness or vertigo is reported as an AE.

4. STUDY OBJECTIVES

4.1. Primary Objective

To assess the long-term ophthalmic safety of tafenoquine Recommended Regimen after 12 months of exposure versus placebo using SD-OCT and qFAF.

4.2. Secondary Objectives

To assess the long-term safety and tolerability of tafenoquine versus placebo as assessed by clinical monitoring of vital signs, ECG, laboratory data, and reporting of AEs after 12 months of exposure.

To assess the long term safety and tolerability of tafenoquine after 12 months of exposure to tafenoquine versus placebo by measuring ophthalmic and psychiatric changes from baseline to end of study.

5. STUDY DESIGN

5.1. Overview

This randomized, double-blind, placebo controlled study will involve 600 healthy (G6PD normal) volunteers and will run in three parts. The Study Site may stagger enrollment of participants into weekly groups to accommodate the screening period.

Part 1 – Treatment phase (52 weeks)

Participants who meet the eligibility criteria will be randomized (ratio 1:1) using clinical site as a randomization variable to receive a loading dose of either tafenoquine 200 mg (2 x 100 mg tablets) or placebo daily for 3 consecutive days starting at Day 1, Week 1 (Visit 2), followed by study treatment (tafenoquine 200 mg or placebo) once per week for 51 weeks with safety follow-up visits at Weeks 4, 12, 24 and 52 (Visits 3, 4, 5, and 6). All efforts will be made to retain participants through to study completion. The reasons for withdrawal may include: 1) withdrawal of consent, 2) lost to follow-up, 3) evidence of substance abuse that may affect the participant's capacity to complete the study in the investigator's opinion, and 4) development of a new or worsening psychiatric disease (including suicidal ideation) at a non-scheduled visit or during routine M.I.N.I. evaluation that would jeopardize the safety of the participant if they continued in the study (see Section 9.2.7). If a participant stops taking their study drug, they should continue to have all follow-up safety visits. If the subject wants to withdraw, they should have an EOS visit (preferably 65-75 days after cessation of study treatment that includes all of the Week 64 assessments). The reasons for any treatment discontinuation (temporarily or permanently) will be documented on the eCRF.

Part 2 – Follow-up phase (12 weeks)

Due to the long t1/2 of tafenoquine (13-15 days with an expected 65-75-day washout period), all participants will return to the clinic at the Week 64 (Visit 7a and 7b) for their EOS visit. If the participant has an ongoing AE, they will continue in Part 3 of the study, otherwise this is the final visit.

Part 3 – Follow-up Phase (every 12 weeks, up to 12 months)

Participants who meet the criteria for continuation for additional safety assessments at Week 64 (Visit 7a and 7b) will continue to be assessed for up to 3 more times at approximately 12-week intervals or until resolution or stabilization of the AE whichever is earlier.

The duration of subject's participation in the study will be up to 110 weeks, including a screening period of up to 6 weeks, a 52-week dosing period, and a 12-week follow-up period. If abnormalities are detected at the 12-week follow-up visit (Week 64 EOS) the subject will continue quarterly follow-up out to 12 months post last dose of IMP. For example, if corneal deposit was the only abnormality found during Week 64, then there is no need to repeat any of the ocular examinations except for corneal photography and corneal slit lamp examination at Weeks 76, 89 or 104 (Visits 8, 9 or 10).

The study will consist of the following for each participant:

- A screening period of up to 6 weeks prior to the first IMP dose. At the first screening visit (Visit 1a), subjects will be screened for eligibility with the exception of the

ophthalmologic assessments. If still eligible after the first visit, the subject will be scheduled for screening and baseline ophthalmic testing (Visit 1b).

- Randomization to receive tafenoquine or placebo in a 1:1 ratio using clinical site as a randomization variable;
- One 200 mg dose of tafenoquine per day for three consecutive days (loading doses; Days 1, 2 and 3) (Week 1, Visit 2) or equivalent dose of matched placebo;
- Once weekly 200 mg doses of tafenoquine or equivalent placebo on Week 2 through Week 52; Follow-up visits on Weeks 4, 12, 24, 52 and 64, and if applicable, Weeks 76, 89, and 104 to follow any ongoing AEs from the prior visit.

5.2. Study Endpoints

5.2.1. Primary Endpoint

Proportion of subjects with protocol-defined SOSE. SOSE is assessed by significant retinal changes from baseline using SD-OCT and qFAF. The details of significant protocol defined retinal changes using SD-OCT and qFAF are defined in Table 5.

5.2.2. Secondary Endpoints

- The incidence, severity and relationship to the IMP of AEs (including unexpected toxicities, AEs encountered during or after IMP administration), safety laboratory parameters, vital signs, and ECG up to and including the end of treatment period Week 52 (Visit 6).
- Mean change from baseline in key SD-OCT parameters including CST, TMV, parafoveal (inner ring of ETDRS grid) retinal thickness and the proportion of participants ellipsoid and interdigitating zone disruption (as per Table 5).
- Proportion of participants with abnormal changes from baseline observed on qFAF using the Spectralis HRA+OCT device with grey scale values extracted from these images for statistical analysis using qFAF software (Heidelberg Engineering).
- Mean change from baseline in BCVA.
- Proportion of participants with corneal deposits from slit lamp examination of the corneal epithelium.
- Time to onset of corneal deposits and overall time duration to resolution post treatment start.
- Time duration to resolution of corneal deposits after treatment cessation.
- Proportion of participants with new abnormalities compared with baseline observed with color retinal digital photography (conventional and wide field).
- Proportion of participants with new abnormalities compared with baseline observed with microperimetry.
- Proportion of participants with any new anomaly on the backlit ETDRS chart.
- Proportion of participants with any clinically significant change in ETDRS BCVA (defined as $\geq$15 letter change [$\geq$ 3 lines] of change in ETDRS BCVA at 4 meters)
- Proportion of participants who develop a color deficiency using the FM-100 hue test.
- Proportion of participants who develop a loss of 0.12 or greater logCS on the Mars letter contrast sensitivity test.

- Proportion of participants who develop a psychiatric disorder in accordance with the DSM-5 as assessed with the M.I.N.I. 7.0.2 assessment questionnaire and suicidal ideation or suicide attempt by C-SSRS interview.
- Proportion of participants with an AE of dizziness or vertigo and severity as assessed by the DHI.
- Mean change from baseline in GTS, QOS, AFS, and BFW as assessed by the LSEQ.

5.3. Rationale of Dose Selection and Dosing Regimen

Previous clinical studies support a Recommended Regimen for malaria prophylaxis of a loading dose of 200 mg once daily for 3 days before travel to a malarious area, followed by weekly 200 mg maintenance doses while in the malarious area and an additional dose of 200 mg at one week of return from travel.

The tafenoquine dose regimen chosen for this study is based on safety and tolerability data, PK data from Phase 1 and 2 studies and efficacy data from dose-ranging chemoprophylaxis studies. The tafenoquine 200 mg dose is regarded as the highest, well-tolerated dose that achieves a protective tafenoquine concentration of 80 ng/mL in 95% of the sample population. Moreover, this is the tafenoquine recommended regimen for malaria prophylaxis approved by the FDA. Results from the placebo arm will be used as a comparator for spontaneous occurrence of ophthalmic and psychiatric effects.

5.4. Individual Subject Withdrawal

All efforts will be made to retain participants through to study completion. Participants may be withdrawn from the study for any of the following reasons: 1) withdrawal of consent, 2) lost to follow-up, 3) evidence of substance abuse that may affect the participant's capacity to complete the study in the investigator's opinion and 4) development of a new or worsening psychiatric disease (including suicidal ideation) at a non-scheduled visit or during routine M.I.N.I. evaluation or reported at an unscheduled visit that would jeopardize the safety of the participant if they continued in the study (see Section 9.2.7).

Participants will be considered withdrawn if they state an intention to withdraw, fail to return for visits, or are lost to follow-up for any other reason. The investigator will make every effort to determine the primary reason for a participant's withdrawal from the study and record this information in the eCRF. For participants who are lost to follow-up, the investigator will demonstrate "due diligence" by documenting all steps taken to contact the participant (e.g., dates of telephone calls) in the source documents.

Unless lost to follow-up, withdrawn participants will be asked to participate in a safety visit as soon as possible after the time that withdrawal has been requested or determined to be in the best interest of the subject and return for a final safety visit 65-75 days after the last dose of tafenoquine (after 5 half-lives tafenoquine clearance). The date of withdrawal in the case of lost to follow-up is the date of the last contact with the subject either in the clinic or by telephone. The date of withdrawal for a subject who withdraws consent is to be reported on the Disposition eCRF as the date of withdrawal; however, if the subject agrees to safety follow-ups, the date of last contact with the subject, as described above, will also be recorded on the eCRF. See section 8.4 for a list of procedures to be conducted at this visit. The reason for treatment discontinuation will be documented on the Drug Compliance eCRF.

5.5. Risk Benefit Evaluation for this Study

The administration of tafenoquine may be associated with unforeseen and serious risks.

Full discussions of the potential risks associated with the administration of tafenoquine are detailed in the Investigator's Brochure (60P IB).

No benefit is expected for individual participants participating in this study. Benefits of the study are society-based and related to possible future antimalarial therapies.

Risks to healthy (G6PD normal), participants in this study will be minimized in the following ways:

- Strict adherence to eligibility criteria will be maintained to ensure that only participants who are not at any perceived risk are enrolled in the study;
- The doses have been demonstrated previously to be safe and tolerable in healthy human participants and within predefined exposure limits;
- Close clinical monitoring to ensure the safety and well-being of the study participants including the following:
  - Exclusion of participants with clinically significant abnormalities from participation in the study at screening;
  - Regular measurements of participants' vital signs (blood pressure, pulse rate, sublingual temperature, respiratory rate);
  - Regular assessment of biochemistry and hematological blood parameters (including liver function tests) will be performed at scheduled time points and repeated, if necessary, to ensure appropriate follow-up of any clinically relevant abnormality.
- The total volume of blood drawn from each participant will not exceed 275 mL during the study (Appendix 3). This volume includes allowance for unscheduled safety laboratory assessments that may be required at the discretion of the PI to ensure participant safety.

5.5.1. Risks/Discomfort to Participants and Precautions to Minimize Risk

Outlined below are anticipated AEs, and a brief description of procedures to ameliorate risks and symptoms. All known risks and precautions described here are explained in detail in the participant information and informed consent form (PIICF).

5.5.1.1. Local Reactions

As the drug is being administered orally, no local reactions are anticipated.

5.5.1.2. Systemic Reactions

Undesirable side effects that have been observed during tafenoquine clinical trials have included the following:

- Blood and lymphatic system disorders, including hemolytic anemia (in patients with G6PD deficiency) and methemoglobinemia.
- Corneal deposits that are fully reversible (within one year). Notably, no treatment-related retinal findings were observed following extended treatment (200 mg x 3 days

loading dose followed by 200 mg/week for 23 weeks) in a Phase 1 clinical safety study (Leary 2009; Study 057).

- GI disorders: nausea, vomiting, abdominal pain and diarrhea.
- Serious hypersensitivity reactions (e.g., angioedema and urticaria) (See also Section 5.5.1.7).

5.5.1.3. Pregnancy

Risks to unborn babies are unknown at this time; pregnant females will be excluded from this study. Female participants should not become pregnant for at least 3 months (5.8 half-lives) after the last dose of IMP. Women of child bearing potential must agree to use an acceptable method of birth control until 90 days following the last dose of IMP.

5.5.1.4. Lactation

Risks to nursing infants are unknown at this time; breastfeeding females will be excluded from this study.

5.5.1.5. Venipuncture

Blood sampling carries a minimal risk of minor discomfort and the possibility of minor bruising at the site of the needle puncture and, rarely, the possibility of infection and radial nerve palsy at the needle puncture site.

5.5.1.6. Ocular Examination and Investigation

Eye examination required administration of topical anesthetic eye drops which stings on initial application. Pupil dilation is required during retinal investigations. This also requires phenylephrine and tropicamide eye drops. All these eye drops are administered during a standard comprehensive eye examination. Blurry vision occurs for up to 4 hours following pupillary dilation. Participants are advised to wear sun glasses and refrain from driving for this period. The risk of angle closure glaucoma is extremely low from pupil dilation. This is further minimized by study procedure that ensures intraocular pressure measurements are taken during ocular examination.

5.5.1.7. Allergic Reaction

As with any IMP administration, no matter what precautions are taken, there is always the risk of serious, or even life-threatening, allergic reaction. Medical emergency equipment is located at the Study Sites. This is available to handle emergencies, such as anaphylaxis, angioedema, bronchospasm, and laryngospasm.

5.5.1.8. Unknown Risks

As with all research, there is the remote possibility of risks that are unknown or that cannot be foreseen based on current information.

5.5.2. Alternatives to this IMP Product or Study

An alternative is not to participate in this study.

5.5.3. Intended Benefit for Participants

This is a study in healthy (G6PD normal) volunteers, thus there is no benefit to the individual or community except the knowledge that the individual's participation has furthered the development of an antimalarial drug.

5.5.4. Risks to the Study Personnel and the Environment

The principal risk in the clinical setting lies in the handling of needles that may be contaminated, the attendant exposure to human pathogens (hepatitis viruses, HIV, and other human pathogens). Adherence to standard operating procedures (SOP) for working with infectious agents and universal precautions will reduce the risk of exposure.

There are no known risks to the environment, other than those associated with the generation of biohazardous waste attendant to drawing blood from humans. All biohazardous waste will be disposed of as stipulated by local, state, and federal regulations and in accordance with study site SOPs.

5.6. Route of Administration, Dosage Regimen, Treatment Period, and Justification

The 600 study participants will be randomized to the tafenoquine or the placebo group in a 1:1 ratio using clinical site as a randomization variable; two groups of 300 participants each will be enrolled in each group.

Each active IMP tablet will contain 100 mg tafenoquine. The dose to be administered orally is 200 mg tafenoquine (2 x 100 mg tablets) per day for three consecutive days (loading doses), followed by another 200 mg dose once per week for the following 51 weeks (beginning post-loading dose Day 10). The placebo group will receive identically-matched double-blind placebo tablets. The IMP tablets will be taken with 180 mL of water but there is no restriction on whether the tablets are taken with or without food.

Safety evaluations will include the following assessments: AE evaluation, physical examination, vital signs, laboratory parameters (hematology, biochemistry, and urinalysis). These will be performed at various time points throughout the study to assess baseline function and any changes from baseline after administration of IMP. Hematology, including methemoglobin assessment, biochemistry and urinalysis will be conducted at Screening, Weeks 4, 12, 24, 52, and 64. Clinical laboratory values indicative of an AE at EOS Week 64 will be repeated during the Follow-up Phase at Weeks 76, 89, 104 until resolution or stabilization.

Previous clinical studies support a recommended dosage tafenoquine regimen for malaria prophylaxis of a loading dose of 200 mg once daily for 3 days before travel to a malarious area, followed by weekly 200 mg maintenance doses while in the malarious area, for a period not exceeding 6 months, and an additional dose of 200 mg at one week of return from travel (60P IB).

In this study tafenoquine will be administered for 12 months to confirm the long term safety of tafenoquine past the 6-month safety window for travelers or military personnel who may be in a malarious area for prolonged periods of time.

5.7. Compliance Statement

The study will be conducted according to the protocol and in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) (CPMP/ICH/135/95), and Belmont Principles (Office for Human Research Protections 1979). All identified study personnel will be trained to perform their roles and will carry out their responsibilities in accordance with ICH GCP guideline and Study Site SOPs.

5.8. Study Sites

This is a multisite study that will be conducted at three sites:

- Linear Clinical Research, Perth, Australia with selected ophthalmologic assessments performed at the Lions Eye Institute, Perth, Australia.
- Retina Consultants of Southern Colorado, Colorado Springs, Colorado, USA
- Valley Retina Institute, McAllen, Texas, USA

6. STUDY POPULATION

Up to 600 healthy (G6PD normal), adult men and women aged 18 to 55 years (age matched to the Study 033 ADF population) will be enrolled in the study.

Participants will be recruited from the Study Site's approved database of healthy participants, or in response to a general or study specific advertisement to students of local universities or the general community, as approved by the local HREC, IRB and HRPO. All racial groups will be included.

After an initial telephone interview conducted by clinical trial staff has occurred to review background information, screening visits will be scheduled over two days. Potential participants will be invited to come to the Study Site. During this initial screening visit, the potential participant will read the participant information sheet and will be encouraged to ask questions regarding the information detailed therein. Participants willing to be considered for inclusion may sign the consent form during the screening visit, or return to the Study Site at a later stage after further consideration. The participant will be given a signed copy of the consent form for their records. The signed and dated originals will be held on file by the Study Site.

After providing written consent to participate, the participant will be examined by the PI or sub-investigator. A detailed medical history will be obtained and a physical examination (including measurements of vital signs and basic ophthalmic testing) will be performed. Blood and urine samples will be collected for safety and eligibility assessments. The participants will be fully informed of the nature of the study at this time, and advised of the requirement to repeat some screening tests as indicated (e.g. see Section 1 Study Schedule of Events) prior to IMP administration.

Eligibility for enrollment will be based on the inclusion and exclusion criteria described below. Participants that fail to meet all eligibility criteria will be excluded from enrollment into the study. The PI or designee will review the screening data and document if a subject meets all of the criteria for enrollment. The PI may also discuss eligibility of a participant with the Local Medical Monitor (LMM).

6.1. Inclusion Criteria

Participants eligible for inclusion in this study must fulfill all of the following criteria:

1. Completion of the written informed consent process (signed).
2. Male or female age 18 to 55 years inclusive, in good health as assessed by the investigator.
3. Normal G6PD enzyme activity levels as defined by the parameters of the specific G6PD test employed at the local laboratory.
4. Negative HBsAg and HCV, HIV-1, HIV-2 antibody screen at the screening visit.
5. Negative serum pregnancy test.
6. Women of child bearing potential must agree to use an acceptable method of contraception from the time of the first administration of the IMP until 12 weeks following administration of the IMP or have undergone a sterilization procedure or are post menopausal. Acceptable birth control methods include:

a. Oral contraceptives (combination estrogen/progesterone pills), injectable progesterone or subdermal implants (commenced at least 14 days prior to IMP administration to the female participant)
b. A medically prescribed topically applied transdermal contraceptive patch (commenced at least 14 days prior to IMP administration to the female participant);
c. Intrauterine device or intrauterine system;
d. Partner uses condom with spermicide;
e. Male partner has had a vasectomy (more than 3 months previously)
f. True abstinence: when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent participants (in consultation with their partners) have to agree to use one of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 90 days after the last dose of study drug.

Acceptable sterilization procedures include:
g. Essure® sterilization;
h. Bilateral tubal ligation;
i. Hysterectomy;
j. Bilateral oophorectomy; or,
k. Be postmenopausal with amenorrhea for at least one year prior to screening and confirmed by a serum FSH test at screening.

7. Willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.
8. Agree to stay in contact with the study site for the duration of the study and up to 2 weeks following the EOS visit (Week 64), provide updated contact information as necessary, and have no current plans to move away from the study area for the duration of the study.

6.2. Exclusion Criteria

Participants fulfilling any of the following criteria are not eligible for inclusion in this study:

1. History of allergy or intolerance to tafenoquine, primaquine or any excipients.
2. History of thalassemia or current or past history of methemoglobinemia, methemoglobin >2% at screening, or hemolytic anemia.
3. Participants with a history of previous eye surgery, is currently using prescription eye drops or has evidence of corneal or retinal abnormalities identified in Screening ophthalmological examination, or by the investigator following review of examination including but not limited to:
   a. BCVA (bilateral) at Screening of <72 letters in either eye;
   b. Eye disease that could compromise assessment of BCVA or imaging of the posterior pole by fundus photography, or SD-OCT, qFAF or is likely to require intervention during the study period (e.g., cataract, glaucoma with documented visual field loss, ischemic optic neuropathy, any inherited retinal disease, nystagmus and any other retinal abnormality or ocular motor disturbance);
   c. History of retinal vascular disease, retinal detachment, diabetic retinopathy, inflammatory disease, central serious chorioretinopathy, color vision impairment

(up to 5% of male population), amblyopia or other retinal disease that may affect posterior retinal function or architecture;
   d. Vitreoretinal interface disorders (e.g. epiretinal membrane, vitreomacular traction) that may affect posterior retinal function or architecture;
   e. History of intraocular surgery;
   f. History of cataract extraction;
   g. History of retinal laser photocoagulation;
   h. History of glaucoma shunt or laser treatment;
   i. History of corneal refractive surgery;
   j. History of high myopia (defined as equal to, or worse than, -8.00 diopters) as well as those with greater than 3 diopters of astigmatism;
   k. Anterior, intermediate or posterior uveitis (active or history of) or history of significant intraocular infectious disease (e.g., endophthalmitis is not acceptable to include) or another active inflammatory disease;
   l. An SD-OCT CSF thickness of <222 µm or >318 µm (Appendix 4).

4. Participants who have recently taken part in, or plan to take part in, any activities or been exposed to conditions which may affect their eyesight (e.g., scuba diving, high altitudes, sun gazing, laser exposure, or ultraviolet [UV] light).
5. Participants whose job performance may be affected by participation in the study (e.g., need to wear night-vision goggles).
6. Participants who, in the opinion of the investigator, do not have the ability to complete the study (e.g. attend all study visits) or to have necessary study investigations performed (e.g. unable to have complete ophthalmic examination as specified in the protocol).
7. Those having received another IMP within 30 days or five half-lives (whichever is longer), of study start.
8. Those having previously received hydroxychloroquine for skin conditions or rheumatological diseases, chloroquine for malaria, tamoxifen, amiodarone or other drugs that may affect the optic nerve/retina/cornea within 30 days or 5 half-lives (whichever is longer) of study start. There are no travel restrictions, but the choice of concurrent anti-malarial must be atovaquone-proguanil if the participant chooses to take a registered antimalarial drug while travelling.
9. Have any of the following, based on DSM-5 criteria as assessed using the MINI:
   a. History of psychotic disorders or current psychotic symptoms (hallucinations, delusions, or grossly disorganized thinking or behavior)
   b. Current (past year) suicide behavior disorder or current (past month) suidicality
   c. or any other current diagnosis of psychiatric disorders . Note: Past history (not diagnosed as current) of a psychiatric disorder within the past year will be referred to the Study Psychiatrist or Psychologist for further evaluation and determination of whether the subject should be excluded from participation in the study. Subjects with a stable past psychiatric disorder, as determined after evaluation by the Study Psychiatrist or Psychologist, may be admitted to the study. If the subject is excluded; the person in question will be referred to their General Practitioner (GP). A subject admitted to the study with a psychiatric history, either self-reported or discovered by M.I.N.I will have their past illness documented in the

medical history eCRF and any current psychiatric medication documented as a concomitant medication.

10. Urine drug screen positive for cocaine, methamphetamine, amphetamines, methamphetamines, barbiturates, benzodiazepines, methadone, opiates, phencyclidine, or tetrahydrocannabinols. Note urine drug screen positive for tricyclic antidepressants or benzodiazepines is allowed if participant reports prescription use for a stable medical/psychiatric condition. Limited use of prescription or non-prescription medications containing codeine and not believed to affect participant safety or the overall results of the study, may be permitted on a case-by-case basis following approval by the Investigator (in consultation with the Medical Monitor, as appropriate).
11. Blood alcohol level > 0.0 determined using an alcohol breathalyzer. Note on interviewing the participant, the investigator may allow enrolment if they are satisfied the participant does not have alcohol dependence and can successfully complete the study protocol. A second blood alcohol test level > 0.0 at Week 1, Day 1 (Visit 2) would constitute grounds for exclusion of the participant.
12. Participants with medical history that might compromise their ability to comply with the protocol.
13. History of cancer (excluding basal or squamous cell carcinomas).
14. Have a clinically significant ECG as determined by the investigator or QTc interval corrected for heart rate using the Fridericia formula (QTcF) > 450 msec.
15. Hemoglobin, platelet counts or neutrophil counts outside the local laboratory reference range and are judged by the investigator to be clinically significant. A laboratory test may be repeated once during screening at the discretion of the Investigator. A subject with a hematology result outside the local laboratory reference range may be admitted to the study if the result is judged as not clinically significant.
16. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total or direct bilirubin, gamma glutamyl transferase (GGT) or creatinine >1.5 times the upper limit of normal (ULN) and are judged by the investigator to be clinically significant. A laboratory test may be repeated once during screening at the discretion of the. If other biochemistry tests fall outside the local laboratory reference range, the subject may be admitted to the study if the out-of-range result is judged as not clinically significant by the investigator.

For other eligibility criteria considerations, the investigator is referred to the IB (60P IB) or current US Prescribing Information for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the use of tafenoquine. The medical monitor should be contacted if the investigator has any questions regarding subject eligibility.

6.2.1. Justification of the Inclusion and Exclusion Criteria

The inclusion and exclusion criteria have been selected to minimize risk to the wellbeing of participants in this study. The criteria are also set to ensure a homogeneous, healthy (G6PD normal) study population that will facilitate the conduct of the study and the scientific evaluation of the study endpoints.

6.3. Subject Identification

All participants who sign the informed consent form will be assigned a unique sequential participant identification number. This will be a 5-digit number (starting at 10001). The participant identification number will be used throughout the study as the primary participant's identifier. The first digit of the subject identifier is the site number.

6.4. Specific Dietary, Fluid and Other Restrictions

6.4.1. General

Participants will be informed and reminded of the following restrictions during recruitment, the informed consent process, and during screening and other scheduled assessments:

Meals and dietary requirements:

- Participants may choose to take the IMP with or without food.

Activity:

- No restrictions.

6.4.2. Concomitant Treatment

General concomitant medication restrictions:

- Tafenoquine may inhibit drug transporters in the kidney. Since inhibition of these transporters may lead to increased exposure to medications that they excrete, when tafenoquine is co-administered with, substrates or inhibitors of MATE or OCT2, it may be advisable to re-evaluate safety and/or efficacy of the latter drugs.
- All participants will be questioned about concomitant medication at each clinic visit. All concomitant medications taken during the study must be recorded with indication, daily dose, route of administration and start and stop dates of administration; and
- Medications taken within 28 days before the first dose of the IMP will be documented as prior medications. Medications taken after the first IMP dose will be documented as concomitant medications.

7. INVESTIGATIONAL PRODUCTS

All IMP are to be used only in accordance with this protocol, and not for any other purpose. The designated study personnel will be provided with adequate quantities of the study IMP (tafenoquine and placebo tablets).

7.1. Description of Products

7.1.1. Investigational Medicinal Product (IMP) - Tafenoquine

Tafenoquine/placebo will be supplied by 60P/USAMMDA in tablet form for oral administration. The IMP products have been manufactured and tested for quality control purposes in accordance with good manufacturing practices (GMP) and local regulations by Piramal Enterprise Limited (India).

Tafenoquine tablets for oral administration are pink, film-coated, capsule shaped tablets containing 125 mg of tafenoquine succinate, which is equivalent to 100 mg of free base.

Tafenoquine tablets also contain: microcrystalline cellulose; mannitol; magnesium stearate; hypromellose; titanium dioxide; iron oxide; and macrogol (also known as polyethylene glycol).

A detailed description of the physical, chemical and pharmaceutical properties of tafenoquine can be found in Section 3 of the 60P IB.

7.2. Packaging, Labeling and Storage

7.2.1. IMP – Tafenoquine and Placebo Tablets

Tafenoquine/placebo tablets are manufactured by Piramal Enterprises Limited, 67-70 Sector II, Pithampur Industrial Area, (Formerly Piramal Healthcare Limited) Pithampur, 454775, India. Tafenoquine and placebo tablets are packed into child-resistant aluminum/aluminum blister packs with 8 tablets per pack.

Investigational products will be provided in drug kits containing 14 blister packs of either tafenoquine tablets or identically matched placebo tablets in each kit. Within each kit, blister packs will be sub-packed into boxes containing, 3, 4, or 7 blisters packs to provide participants with sufficient IMP between dispensing visits, plus enough extra tablets for the study windows, so there should be no interruptions in dosing. Packaging and shipment of clinical supplies to the site will be performed by Catalent, Inc., Philadelphia, USA. Each kit will contain a total of 112 tablets, thus providing a sufficient supply of tablets for the entire study for a single participant in one kit plus 4 extra tablets. The content of the labeling will be in accordance with the TGA GMP requirements (Annex 13 of PIC/S 2009) and the label will include information regarding the identity (blinded), lot number, expiry date and storage conditions (both tafenoquine and placebo to maintain the blind). Drug kits used in the United States will have additional labeling in accordance with FDA requirements (i.e., “Caution: New Drug – Limited by Federal Law to Investigational Use”). Kits will have a sequential numeric code to blind the identity of the IMP and will be randomly assigned to participants by kit number.

Tafenoquine is marginally light sensitive. Tafenoquine can be transported and stored at ambient room temperature (i.e., between $\geq$15 and $\leq$25°C), protected from light, in a secure

location accessible to authorized personnel only. Storage conditions must be adequately monitored and appropriate temperature logs maintained throughout the study while IMP is stored at site. Temperature excursions are permitted to 15°C to 30°C (59°F to 86°F). Participants will be instructed to store their IMP in a cool, dry place out of reach of children. The aluminum/aluminum blister packaging protects the IMP from light.

7.3. Investigational Medicinal Product Accountability

The designated study personnel, as nominated by the investigator, are responsible for maintaining accurate IMP accountability records throughout the study. Dispensing, accountability and documentation will be in accordance with the Study Site standard SOPs. All products will be inventoried upon receipt by the study site designated study personnel. The condition of the products at the time of receipt by the site staff will be documented.

IMP and study accountability logs will be available to the sponsor or sponsor's representative as part of the study monitoring procedures. Upon completion of the study, copies of all study drug management records will be provided to the sponsor. Original records will be maintained at the Study Site with the rest of the site study records.

7.3.1. Medication Adherence and Reminder System

This study will employ a medication adherence reminder platform electronic text messaging system (Mosio) for all participants in the study. This system uses electronic text messaging reminders to notify subjects when to take their daily or weekly doses.

Use of this system will in no way supersede or replace the study PI and/or prescribed medication protocol of the participants. Because the system does not change the medication protocol of the participants, but rather encourages adherence to the predefined protocol, use of this system presents minimal risk to the participants. Use of the system will be required for all participants in the study.

When at home, study participants will receive an automatic text message medication reminder at a time within a predefined window. This notification reminds participants to take their medication dose and has the functionality to record the date, time, and number of tablets taken. There is no need for a healthcare provider to review the administration, nor would a healthcare provider need to be available at the time the participant takes their medication.

The system is compliant with the Health Insurance Portability and Accountability Act (HIPAA), which protects the privacy and security of healthcare information. Phone numbers of the participants may also be collected and stored in an encrypted manner. Storing the phone numbers will allow for direct communication with participants, including automated messaging from the system web application and contact by study staff. At no time is the phone number visible to anyone within the system. Individuals outside the clinical sites will not be provided with subject names, nor will they be given access to subject research records. The system may provide significant benefits to study participants as well as to the other stakeholders in the trial. Study staff will have access to real-time and continuous adherence data without having to rely on self-reported data or frequent study visits by participants. Participants who regularly fail to take their medication will be contacted by study staff for retraining.

7.3.2. Participant Risk

The Mosio system provides no more than minimal risk to participants. This system only introduces a smartphone-based text messaging application that reminds the user to take their medication, reminds the user of their next scheduled clinic visit, and stores encrypted data (date, time, and number of tablets taken) securely for analysis.

All study data, including any identifiable patient information, will be obtained and encrypted by the application. Participants will be identified by their subject identification number assigned to them for the study. After the subject has taken the medication and record is made in the system, the encrypted data will be automatically forwarded to a secure server. The server is compliant with the HIPAA, which protects the privacy and security of healthcare information. The data will be securely stored and only accessible authorized personnel through two-way authentication.

7.3.3. Patient Confidentiality

The Mosio system will protect participants' personal information to the full extent required by law. However, information from this study, will be collected at the study site, and potentially provided to the US FDA or other national regulators. Both information obtained by the application and information in the consent form, may be examined by the study site or the study site's representatives, and may also be reviewed by the FDA and other regulatory agencies, and or HREC/IRB and HRPO. All of these parties are bound to safeguard the rights, safety and well-being of all clinical trial participants, and to maintain all information in confidence.

7.4. Method of Assigning Participants to Treatment Groups

Participants will be assigned to receive either tafenoquine or placebo in a 1:1 ratio using clinical site as a randomization variable with a permuted block randomization procedure in accordance with a randomization schedule generated by a Fast-Track Biostatistician.

Centralized randomization will be performed using the electronic data management system (EDMS), (IBM Clinical Development) that contains a randomization module. The EDMS is available for randomization of participants 24 hours per day, 7 days per week from any computer using a web browser.

If the participant is determined to be eligible, site personnel who are authorized to randomize participants and who have completed training for the IWRS, will log onto the system and provide the pre-assigned unique participant number. The IWRS provides the randomized group kit number and assigns the participant to one of the two interventions. If the participant is randomized and is never dispensed study drug, then the participant will be considered a randomization failure and an additional participant will be randomized with the next randomization sequence at the time he/she is randomized at that site. Likewise, if the participant was randomized and then is determined to not be eligible for the study, and never received study drug, then another participant will be randomized such that the total numbers of participants who were eligible, randomized, and dispensed study drug meet the enrollment goals.

7.5. Investigational Product Administration

7.5.1. Tafenoquine/Placebo

Participants who are randomized to receive tafenoquine/placebo will be dispensed sufficient blister packs and of the assigned IMP for administration between study visits. The participant may take the initial dose of the IMP after randomization, while still in the clinic. IMP may be taken with or without food.

Subjects are provided with a diary card at randomization that contains the instructions for dosing and a place for the subject to record doses taken. The subject will be asked to return the blister packs and the diary card at each clinic visit for accountability. The electronic text messaging system will be used to send participants reminders to self-administer IMP and record the date, time, and number of tablets taken. Although the Mosio system does allow the participant to record the number of tablets taken, the platform is only intended to remind the participants to take medication and compliance data collected via the text messaging system will be available to site staff for the sole purpose of confirming drug compliance in between in clinic visits. In the event site staff notes subject non-compliance in between clinic visits, site staff should contact the subject and counsel the subject on proper medication compliance. Data will be reviewed weekly and follow-up text messages may be sent if the subject is missing doses. The diary card will be examined during each clinic visit and reconciled against the blister packs.

The number of tablets and date and time administered will be recorded in the eCRF.

7.6. Treatment Blinding

The study is double-blinded. As the tafenoquine and placebo tablets are identical in appearance, and the IMP is provided to the site in blind coded drug kits, all research staff and participants will be blinded.

7.7. Unblinding

Any accidental unblinding should also be reported in writing to the sponsor and LMM. The report should include the reason for the unblinding and the steps taken to ensure that the risks of this happening again in the future are minimized.

Special care should be taken to keep the participants masked when examining study physician notices and documents relating to corneal deposits or when the photographer is taking images of these benign changes since these lesions are indicative of tafenoquine exposure and they have no visual consequences, participants should not be told when these deposits are identified during any study visits.

The PI or designated approved study physician will make the decision to un-blind the identity of the IMP in the event that the study blind needs to be broken to make medical decisions regarding participant treatment. If it is determined that unblinding is necessary to assess AEs or SAEs for expedited reporting, the sponsor may decide to request unblinding of a participant. Site staff or sponsor's designee approved to un-blind the IMP for an individual participant will log into the IWRS to obtain the name of the IMP to which the participant was randomized. The IWRS will automatically notify the un-blinded staff member at the Data Management Site who will notify the sponsor. The sponsor will be notified that an unblinding has occurred if unblinding has been performed by the investigator or designee.

7.8. Returns and Destruction

Used and unused blisters will be destroyed at the site once drug accountability is final and has been checked by the assigned study monitor, and written permission for the destruction has been obtained from the sponsor. Details of the final disposition of the study drug, including a copy of the destruction certificate as relevant, will be documented in the site study file.

8. VISIT SCHEDULE

A summary of the schedule of events for the study is presented in Section 1 Study Schedule of Events.

8.1. Screening: Week -6 to Day -1 (Visit 1a and 1b)

Participants will be recruited for screening and consented as described in Section 6 over an up to 6 week period. Participants will be assessed for safety laboratory testing on Day 1 of screening (Visit 1a). Clinical laboratory tests may be repeated one time at the discretion of the investigator a repeat test is warranted to assure subject eligibility. If the participant passes these preliminary tests (i.e., not meeting exclusion criteria), they will be further assessed at a second screening visit (Visit 1b) by thorough ophthalmic testing with and without pupil dilatation. Assessments in the schedule for the 1b visit may be conducted at the 1a visit or any 1a or 1b visits may be conducted on different days within the 6-week period at the convenience of the clinical site and the subject. The 1b visit includes visual function tests, ocular biometry, slit lamp examination, microperimetry, and retinal imaging, to confirm that no final ophthalmic exclusion criteria exist for the participant prior to enrollment. The ophthalmic testing procedures on Visit 1b are more time consuming and some procedures require the pupils to be dilated using phenylephrine and tropicamide eye drops. Blurry vision occurs for up to 4 hours following pupillary dilation at this second screening visit. All screening assessments will be performed during the period from 6 weeks to up to the first IMP dose.

The following information will be obtained and assessments performed during this time:

- Signed, written informed consent as detailed in Section 6;
- Initial review of inclusion and exclusion criteria by the investigator to confirm eligibility for screening;
- Collection of demographic data;
- Collection of body height and weight data;
- Medical and surgical history and details of current medications (including herbal products and nutritional supplements);
- Social history of previous and current tobacco, alcohol use and drugs of abuse;
- A complete physical examination;
- Vital signs (blood pressure, pulse rate, respiratory rate and sublingual body temperature) after the participant has been resting in a seated position for 5 minutes;
- 12-lead ECG;
- Blood sampling for determination of the following parameters
    - CBC;
    - Biochemistry;
    - G6PD testing;
    - Methb%;

- Serology (HBsAg, HCV, HIV-1 and HIV-2 antibodies);
- Serum ß-HCG pregnancy or FSH test (WOCBP or post-menopausal females only);

- Alcohol breath test;
- Urine sampling for determination of the following parameters:
  - Urinalysis (dipstick and urine microscopy if blood, leukocyte esterase, or nitrates are positive); and
  - Urine drug screen (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tetrahydrocannabinols, and tricyclic antidepressants).
- **Ophthalmic Assessments**: The following ophthalmic tests will be performed at Screening. Given the short period of time between Screening (Visit 1b) and dosing (Week 1, Day 1 [Visit 2]) the ophthalmic data from Screening will be used as the baseline data:

  Visit 1b:

  Before pupil dilation:
  - BCVA (ETDRS letter score);
  - Color vision assessment with FM-100 hue test;
  - Mars letter contrast sensitivity test;
  - M-chart distortion test; and
  - Slit lamp examination.

  After pupil dilation:
  - MAIA microperimetry. Conducted twice with the first result discarded to minimize learning effect.
  - Heidelberg Spectralis SD-OCT (including wide field macular scan);
  - Heidelberg Spectralis qFAF (set of 3 images to ensure consistency in measurement);
  - Digital photograph of corneal surface (conventional and wide field);
  - Digital photograph of retina (conventional and wide field);
  - Slit lamp retinal examination (pupils dilated) and intraocular pressure (IOP) measurement
- **Psychiatric Assessments**
  - M.I.N.I. English Version 7.0.2.
- **Eligibility Assessment by Investigators:**
  - Final review of inclusion and exclusion criteria by the investigators to confirm eligibility for enrolment into study;

Participants who complete all screening procedures and satisfy all eligibility criteria will be considered eligible to participate in this study.

If screening laboratory results are abnormal (after repeat tests as appropriate are performed) (e.g., HIV testing), the participant will be referred for appropriate counseling as applicable. If any clinically significant abnormalities are detected during screening, the participant will be referred for follow-up tests to a general practitioner or medical specialist as appropriate.

8.2. IMP Loading Dose: Starting Day 1 of Week 1 (Visit 2)

Participants will report to the Study Site on the morning of Day 1. After completion of the pre-dose assessments, they will receive a single dose of tafenoquine or placebo with water and their first participant drug pack will be issued. Participants will be advised to take doses 2 and 3 in Week 1 at home. The following week, the participant will need to take their dose (2 x 100 mg tablets) commencing 7 days after their last loading dose on Day 3 of Week 1 and continue weekly (every 7 days), thereafter.

The following information will be obtained prior to randomization to collect baseline data and confirm continued eligibility:

- Confirmation of consent/signed informed consent.
- Update information regarding any new medical conditions, medicines (including herbal products and nutritional supplements), surgery or illnesses since screening.
- Update information on social history since screening.
- C-SSRS interview.
- Abbreviated physical examination (pre-dose). A symptom-directed physical examination may also be performed if it is required according to the opinion of the investigator.
- Vital signs (blood pressure, pulse rate, respiratory rate and sublingual body temperature) after resting in a seated position for 5 minutes (pre-dose).
- Blood sampling for determination of the following parameters:
  - CBC, MetHb% and biochemistry; and
  - PK blood sample for tafenoquine.
- Alcohol breath test.
- Urine sampling for determination of the following parameters:
  - Urine pregnancy test (β-HCG) (pre-dose, WOCBP participants only);
  - Urinalysis (dipstick and urine microscopy if blood, leukocyte esterase, or nitrites are positive);
  - Urine drug screen (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tetrahydrocannabinols, and tricyclic antidepressants); and
- DHI assessment (only collected in participant reports AE of dizziness or vertigo).
- LSEQ assessment.
- Inclusion/exclusion criteria confirmed.

The following will be performed after continued eligibility is confirmed:

- Randomization number obtained by IWRS;
- IMP administration (2 tablets with water).
- Dispense investigational product and provide instructions on use of diary card and text messaging reminder and compliance system.

After completion of the assessments and after administration of the tafenoquine dose, participants will be allowed to leave the Study Site if they are considered to be in good health by the investigator.

8.3. Treatment Period: Week 4, 12, 24, and 52 (Visits 3, 4, 5 and 6)

Participants will report to the Study Site in the morning.

The following assessments will be performed over the treatment period:

- Abbreviated physical examination- a symptom-directed physical examination will be performed based on signs and symptom the participant has reported verbally. A symptom-directed physical examination may also be performed if it is required according to the opinion of the investigator.
- Vital signs (blood pressure, pulse rate, respiratory rate and sublingual body temperature).
- 12-lead ECG (Week 4 and 52).
- Blood sampling for determination of the following parameters:
  - CBC;
  - Biochemistry;
  - MetHb %;
  - Plasma for PK analysis;
- Urine sampling for determination of the following parameters:
  - Urine ß-HCG pregnancy test (WOCBP only) at Weeks 4, 12, 24 and 52;
  - Routine urinalysis (dipstick and urine microscopy if blood, leukocyte esterase, or nitrites are positive); and
  - Urine drug screen (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tetrahydrocannabinols, and tricyclic antidepressants);

Ophthalmic Assessments: The following ophthalmic tests will be performed routinely during the Treatment Period at Weeks 12, 24 and 52 Ophthalmic assessments may be scheduled as a second visit during weeks when most of the examinations are performed to not overburden the length of the visit for subjects.

Before pupil dilation:

- BCVA (ETDRS letter score);
- Color vision assessment with FM-100 hue test;
- Mars letter contrast sensitivity test;

- M-chart distortion test; and
- Slit lamp examination and corneal deposit grading (the Orlando system).

After pupil dilation:

- MAIA Microperimetry (only Weeks 24 and 52);
- Heidelberg Spectralis SD-OCT (including wide field macula scan);
- Heidelberg Spectralis qFAF (set of 3 images to ensure consistency in measurement);
- Digital photograph of corneal surface (conventional and wide field);
- Digital photograph of retina (conventional and wide field);
- Slit lamp retinal examination and IOP measurement; and

- **Psychiatric Assessments**
  - M.I.N.I. English Version 7.0.2;
  - DHI (only if a participant reports AE of dizziness or vertigo); and
  - LSEQ.
- Recording AEs and any concomitant medications.
- Electronic compliance system, diary cards and used blister packs checked. Number of tablets taken, date and time recorded in eCRF. Diary cards and final used blister packs collected at Week 52.

Also every 4 weeks ± 1 week during the treatment period, a C-SSRS interview will be conducted either by telephone at any time or in person at a clinic visit at the discretion of the site staff.

8.4. Early Termination/EOS assessments, Weeks 64 (Visit 7a and 7b)

This visit scheduled to occur during Study Week 64, will be conducted over two days during this week to complete all assessments. Data will be recorded at the nominal Week 64 visit.

Due to the long $t_{1/2}$ of tafenoquine (13-15 days with an expected 65-75-day washout period), all participants will return to the clinic at Week 64 for their EOS visit. If a participant withdraws prematurely; all these study checks should be completed at the final outgoing visit, preferably 65-75 days after their last dose of IMP:

- Full physical examination;
- Vital signs (blood pressure, pulse rate, respiratory rate and sublingual body temperature);
- 12-lead ECG;
- Blood sampling for determination of the following parameters:
  - CBC and biochemistry;
  - MetHb %;
  - Serum β-HCG pregnancy test (WOCBP only);

- Urine sampling for determination of the following parameters:
  - Urinalysis (dipstick and urine microscopy if blood, leukocyte esterase, or nitrites are positive); and,
- **Ophthalmic Assessments**:

  Before pupil dilation:
  - BCVA (ETDRS letter score);
  - Color vision assessment with FM-100 hue test;
  - Mars letter contrast sensitivity test;
  - M-chart distortion test; and
  - Slit lamp examination;

  After pupil dilation:
  - MAIA microperimetry;
  - Heidelberg Spectralis SD-OCT (including wide field macula scan);
  - Heidelberg Spectralis qFAF (set of 3 images to ensure consistency in measurement);
  - Digital photograph of corneal surface (conventional and wide field);
  - Digital photograph of retina (conventional and wide field);
  - Slit lamp retinal examination and IOP measurement
- **Psychiatric Assessments**
  - M.I.N.I. English Version 7.0.2;
  - DHI (only if a participant reports AE of dizziness or vertigo); and
  - LSEQ.
- Recording AEs and any concomitant medications.

Also every 4 weeks ± 1 week between the Week 52 and the Week 64 visit, a C-SSRS interview will be conducted.

8.5. Part 3 Follow-up for Ongoing AEs Weeks 76, 89, and 104 (Visits 8, 9, and 10):

The following are the criteria for participant continuation for additional safety assessments:

- Ongoing AE.
- Laboratory value is determined to be a new or continuation of an ongoing AE.
- Diagnosis of psychiatric disorder.
- Abnormality found on any of the following ophthalmologic examinations (only the test that revealed an abnormality will be repeated, unless at the discretion of the investigator additional testing is warranted):

  - SD-OCT, qFAF, BCVA [ETDRS], FM-100 hue test, Mars letter contrast sensitivity test and M-chart.
  - Slit lamp examination and digital photograph of corneal surface (cornea Verticillata) and retinal digital photograph (toxic maculopathy and retinopathy on conventional and wide field device).
  - Microperimetry.

Participants will report to the Study Site in the morning.

The following assessments will be performed during this follow-up visit (if required):

- Blood sampling as needed to follow abnormality:
  - CBC and biochemistry;
  - MetHb %;
- Urine sampling as needed to follow abnormality:
  - Urinalysis (dipstick and urine microscopy if blood, leukocyte esterase, or nitrites are positive).
- Ophthalmic Assessments (repeat only if abnormal at Week 64). Abnormal results may need to be further investigated using microperimetry, color vision assessment with FM-100 hue test, Mars letter contrast sensitivity test and M-chart. Corneal deposits and retinal lesions from drug toxicity at Week 64 needed to be monitored by slit lamp examination, SD-OCT (including wide field macula scan), qFAF and photography (conventional and wide field);
- Psychiatric Assessment with M.I.N.I 7.0.2 (repeat if disorders are found at Week 64).
- Assessment with DHI (if participant reports ongoing AE of dizziness or vertigo).

General:

At all follow-up visits, participants will be reminded of the following before leaving the Study Site:

- Study restrictions as described in Section 6.4;
- To return to the Study Site for the following scheduled visit; and
- To contact the Study Site in the interim should they experience AEs or require treatment with any concomitant medications.

8.6. Assessment and Visit Windows

The following time-related windows will be acceptable based on logistical and operational considerations:

- Out Patient Week Visits: as follows, unless otherwise indicated by the investigator:
  - Week 4 $\pm$ 3 days (Visit 3);
  - Week 12 $\pm$ 2 weeks (Visit 4);
  - Week 24 $\pm$ 2 weeks (Visit 5);
  - Week 52 $\pm$ 2 weeks (Visit 6);

- Week 64 ± 2 weeks (Visit 7a and 7b)

AND if ongoing AEs are being followed;

- Week 76 ± 2 weeks (Visit 8).
- Week 89 ± 2 weeks (Visit 9).
- Week 104 ± 2 weeks (Visit 10).

At all-time points where multiple assessments are performed and blood samples are collected, vital signs measurements (when relevant) will be performed before blood sampling.

Any deviations from the above-mentioned permissible window periods will be documented as protocol non-compliances and will be evaluated for significance at the data review meeting prior to database lock.

8.7. Unscheduled Visits

In the event that a participant reports a potential AE by telephone or other means in between regularly scheduled visits, an unscheduled visit may be performed to do a more detailed analysis of the event. The assessments to be performed at unscheduled visits are at the discretion of the investigator but could include for example, a repeat M.I.N.I. examination if the subject reports a new psychiatric symptom or to repeat any questionable ophthalmic test results that may need to be repeated or validated (Marmor 2016).

Additional unscheduled visits could also include repeat clinical laboratory tests in the event that a result is indicative of a clinically significant finding to assist in the determination of the resolution of an AE. Another case would be if a subject was found to have an unexplained marked reduction of visual acuity ≥15 letters (≥ 3 line change) of ETDRS BCVA at 4 meters (an AESI) and a repeat BCVA test was warranted sooner than the next scheduled visit.

9. ASSESSMENTS

9.1. Screening and pre-IMP dosing Assessments

Unless noted otherwise, the window period within which all screening evaluations must be completed, and the results reviewed by the investigator to confirm eligibility of participants, is from 6 weeks to one day prior to dosing with IMP. Baseline evaluations (with the exception of those tests that are only performed at the first screening visit) will be regarded as those performed immediately prior to IMP dose administration on Day 1 (Week 1 [Visit 2]).

9.1.1. Demographics

Participant demographic and baseline characteristic data to be collected on all participants include: date of birth, age, sex and race/predominant ethnicity.

9.1.2. Height and Weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kg in indoor clothing, but without shoes) will be measured.

9.1.3. Medical, Surgical and Current Medical Conditions

Participants will provide a detailed medical, surgical, and medication usage during screening and again prior to IMP administration, in order to assess the eligibility of the participant for the study.

Any event or change in the participant's condition or health status prior to the initial administration of the IMP will be reported in the relevant medical history/current medical conditions section of the eCRF and not as an AE pre-dose.

9.2. Safety

9.2.1. Physical Examination

A complete physical examination will include:

- General appearance;
- Skin;
- Head, neck (including thyroid), ears, eyes, nose, mouth (including dentition), throat;
- Heart
- Circulation;
- Chest;
- Lungs;
- Abdomen;
- Back;
- Extremities;
- Lymph nodes; and

- Neurological examination.

After screening evaluations, an abbreviated, symptom-directed physical examination will be performed focused on changes since the previous examination, but will always include at least:

- General appearance;
- Skin;
- Heart / circulation;
- Chest / lungs;
- Abdomen; and
- Brief neurological examination.

Significant findings present prior to the administration of the IMP will be recorded in the relevant medical history/current medical conditions section of the participant's eCRF. Significant findings made after these time points and which meet the definition of either an AE or a disease-related event, will be recorded as such in the relevant section of the participant's eCRF.

9.2.2. Vital Signs

Vital signs including blood pressure, pulse rate, respiratory rate and sublingual body temperature after the participant has been resting for 5 minutes in a seated position as stipulated in the study schedule (Section 1 Study Schedule of Events).

The vital signs' normal ranges will be defined by site.

9.2.3. 12-lead ECG

Standard, 12-lead ECGs will be performed at Screening and nominal Weeks 4, 52, and 64. The clocks on all ECG machines will be synchronized with the central clock on a daily basis. Participants will rest for at least 5 minutes prior to the start of recording. ECG tracings will be retained and labeled as per SOPs at each clinical site.

Real-time interpretation of the tracings will be made on-site with special attention being given to changes in PR-, QRS- and QT-intervals as well as T-wave morphology changes and dysrhythmias. The QTc interval corrected for heart rate using the Fridericia formula [$(QTcF = QT/RR)^{(1/3)}$] (Fridericia 1920) will be calculated. Any change > 450 msec will be considered clinically significant. Any clinically significant findings will be discussed with the LMM and sponsor. The investigator will sign and date each ECG as evidence of their review.

9.2.4. Laboratory Evaluations

Evaluations of standard laboratory parameters will be performed as part of the screening and baseline determinations of eligibility, as well as throughout the follow-up period as part of the safety assessments. Details of the timing of these evaluations are presented in Section 1 Study Schedule of Events and in Section 8 Visit Schedule.

The investigator will document the clinical significance of all results falling outside of the normal reference ranges. All abnormal laboratory test results judged as being clinically significant by the investigator, will be reported to the LMM (and in turn the Data Safety Monitoring Board [DSMB]) and will be recorded as an AE. Repeated evaluations are

mandatory until normalization of the result(s) or until the change is no longer considered clinically significant.

Hematology

The following standard parameters will be assessed at all relevant time-points:

- RBC count, Hb, Hct, MCH, MCV, Plt count, WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils); and

A manual blood smear will be reviewed if immature/abnormal cells are detected on the automated differential or if an automated differential is not able to be performed

- MetHb %.

The methemoglobin assay is only performed at Clinipath's laboratory at the Mount Hospital (in Australia). Due to the short sample stability requirements, this sample must be routed/shipped to the Mount Hospital (or US equivalent laboratory) within 90 minutes of collection, to ensure analysis occurs within the 4-hour stability window period. An optical absorbance measurement will be taken using a Gem4000 analyzer (or equivalent). The Final Clinical Study Report (FCSR), will document the assay(s) used to measure methemoglobin.

Biochemistry

The following parameters will be measured at all relevant time-points:

- BUN, creatinine, potassium, sodium, AST, ALT, ALP, GGT, total and direct bilirubin.

Serology and other special laboratory investigations

- All participants will be screened for HBsAg, anti-HCV, anti-HIV-1 and anti-HIV-2 antibodies (if positive confirmed by a second test as per laboratory protocol).
- G6PD status will be determined at Screening.

Alcohol breath test, urine drug screen

- A urine screen for drugs of abuse (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tetrahydrocannabinols, and tricyclic antidepressants); and
- An alcohol breathalyzer test (Screening [Visit 1a] and Week 1, Day 1 [Visit 2] only).

Urinalysis

Urine will be collected for dipstick analysis with microscopy, as applicable, by a specified study lab.

The following parameters will be assessed: specific gravity, pH, glucose, protein, blood, ketones, leukocyte esterase, and nitrates. Microscopic examination will be performed if blood, leukocyte esterase, or nitrates are positive. Culture and sensitivity will be performed, if indicated, by the microscopy results.

Pregnancy

All WOCBP participants will have a serum β-HCG measurement at Screening and the Week 64 EOS visit. A urine β-HCG test will be undertaken prior to first IMP dose (Week 1 [Visit 2]) and at Week 4, 12, 24 and 52 visits.

Females who are menopausal will have this status confirmed by a serum FSH test at Screening.

If a participant is found to have a positive urine pregnancy test at any stage during the study, a confirmatory serum β-HCG will be performed. If confirmed positive, the participant will be discontinued from IMP and followed as described in Section 10.11.6.

9.2.5. Pharmacokinetics for Compliance

Blood samples will be collected from Week 1 to Week 52 either by direct venipuncture or via an indwelling cannula inserted in a forearm vein into an ethylene diamine tetra-acetic acid (EDTA) purple top tube.

The actual sample collection date and time will be entered in the PK blood collection section of the eCRF. Any sampling problems will be documented in the eCRF.

The parent drug in the plasma samples will be analyzed using bioanalytical assays validated to meet both European Medicines Agency (EMA) or FDA requirements (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2** and FDA 2001). Assays will be performed and the methodology will be detailed by the bioanalytical laboratory.

9.2.6. Ophthalmic Assessments

The ophthalmic assessments will be conducted at Screening at (Visit 1b or 1a depending on site and subject preference) and repeated at Weeks 12, 24, and 52 of the Treatment Phase and at the EOS visit (Week 64). Ophthalmic assessments will be repeated at Week 76 (Visit 8) and quarterly thereafter to 12 months if ongoing or new ophthalmic abnormalities are identified at the Week 64 visit. Microperimetry testing will be conducted at Screening twice with the first result discarded to minimize learning effect and at Weeks 24, 52 and 64. Non-clinically significant abnormalities at Baseline (Week 1, Day 1) will be recorded as medical history and will only be followed up after Week 64 if the abnormality worsens during the Treatment Period.

Please note, only tests that are abnormal at the Week 64 visit will be followed up in Weeks 76, 89 or 104 (Visits 8, 9, or 10). For example, if corneal deposit was the only abnormality found during Week 64, then there is no need to repeat any of the ocular examinations except for corneal photography and corneal slit lamp examination at Weeks 76, 89 or 104. Therefore, not all ophthalmic testing will need to be completed in Phase 3 of the study at the discretion of the PI.

Specific test parameters will be provided in the ophthalmology manual for the study.

Routine ophthalmic tests will include the following:

- BCVA (ETDRS);
- Color vision assessment with FM-100 hue test. The Lanthony D15 test will be administered immediately prior to the FM-100 test to reduce learning affects.
- Mars letter contrast sensitivity test;
- M-chart;
- Slit lamp examination of anterior and posterior segment
- Intraocular pressure measurement
- Microperimetry (Weeks 24, 52 and 64).

- SD-OCT (including wide field macula scan);
- qFAF (set of 3 images to ensure consistency in measurement);
- Digital photograph of corneal surface (conventional and wide field); and,
- Digital photograph of retina (conventional and wide field)

Abnormal results may be further investigated using microperimetry, FM-100 hue test, Mars contrast sensitivity letter reading test, M-chart, slit lamp examination, SD-OCT (including wide field macula scan) and qFAF depending on the nature of the abnormality.

The Lions Eye Institute in Australia or the Retinal Institutes in the US will provide clinical site training materials, certifications of the readers and will perform the initial evaluation of SD-OCT, qFAF and color photos for both eyes. Color photos of the cornea and retina will be used as complementary images. The evaluations performed at these sites will be used for initial reporting of ophthalmologic AEs and SOSEs.

The University of Wisconsin School of Medicine and Public Health, Fundus Photograph Reading Center will perform a masked (the site's evaluation will not be provided) evaluation of SD-OCT, qFAF and color photos for both eyes. Prior to the start of the clinical trial, they will provide training of operators in the form of written instructions for acquiring digital images for SD-OCT, qFAF and color images permit uploading digital images into their EXCELSIOR™ data management platform as well as certification of the readers and the equipment prior to transfer of images to the Fundus Photograph Reading Center for evaluation. They will evaluate SD-OCT and qFAF scans for qualitative and quantitative assessment per protocol-defined outcomes. Color photos will be used as complementary images. On a monthly basis, they will perform data transfer to Fast-Track for inclusion in the main study database. In addition, they will maintain HIPAA and 21 Code of Federal Regulations (CFR) Part 11 compliant computer services with a technical support help desk for users uploading images to the EXCELSIOR™ data management platform.

After data transfer, results from the clinical sites will be compared with that at the Fundus Reading Center by the data management center and the results of the comparison will be provided to the site PI for review.

9.2.7. Psychiatric Assessment (M.I.N.I. 7.0.2)

The administration of the M.I.N.I. 7.0.2 will be performed by designated staff or consulting clinical psychologists trained to administer the questionnaire to study participants. The study Psychiatrist or Psychologist (nominated in the study delegation log) will be consulted for definitive diagnosis in the event that that M.I.N.I. is indicative of a psychiatric disorder.

The M.I.N.I. was designed as a brief structured interview in accordance with the DSM-5 and the International Classification of Diseases (ICD)-10. Validation and reliability studies have been done comparing the M.I.N.I. to the longer Structured Clinical Interview for Diagnostics (SCID)-P for DSM-III-R and the Composite International Diagnostic Interview (CIDI) (a structured interview developed by the World Health Organization [WHO]). The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments (Amorim 1998).

Any new or worsened psychiatric disease identified at a non-scheduled visit or during the routine M.I.N.I. assessment procedures (including suicidal ideation) will be referred to the

Study Psychiatrist or Psychologist for further evaluation as needed to make a diagnosis and capture and record AE severity and causality. As with all AEs, appropriate care and evaluation will be made in coordination with the LMM which may include further referral and/or hospitalization as required. These AE's will continue to be followed until they are resolved or stabilized. Decisions regarding the participant's continuation in the study will be made by the Study Psychiatrist or Psychologist in consultation with the study PI and LMM.

9.2.8. Leeds Sleep Evaluation Questionnaire (LSEQ)

The LSEQ is a participant assessment of the difficulty of falling asleep, quality of sleep, awakening from sleep, and behavior following wakefulness as these factors can be causative or related to psychiatric disorders (Zisapel 2003). This questionnaire was developed as a clinical investigation tool to retrospectively measure sleep patterns prior to study participation.

9.2.9. Dizziness Handicap Inventory (DHI)

Dizziness is common symptom that is reported frequently with varying degrees of impact on the individual's quality of life. Dizziness can be caused by many different clinical conditions. While the impact of dizziness is predictive, this disorder can be more consistently evaluated by using a tool such as the DHI. The DHI is a reliable, comprehensively validated and clinically useful tool to measure self-perceived handicap associated with the symptom of dizziness from a variety of causes (Treleaven 2005).

Participants who admit to new or worsening dizziness or vertigo during their routine AE monitoring queries will rate the severity of the dizziness using the DHI. The self-administered questionnaire takes 5-10 minutes to complete and doesn't require special training to administer. Respondents choose the statement that most describes them. The statements are scored from 0 – 4 and scores can range from 0 – 100 (Whitney 2004). The questionnaire will be self-administered and scored by the designated study personnel. The DHI has been validated and can detect statistically significant change over time in group data (Enloe 1997).

9.2.10. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a 2-page form (Appendix 7) asking questions about suicidal ideation, intensity of ideation, and suicidal behavior developed by Posner and collaborators at the New York State Psychiatric Institute (Oquendo-2003). This scale is intended for use by trained administrators. The questions contained in the C-SSRS are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment. Training is required before administering the C-SSRS through a 30-minute interactive slide presentation followed by a question-answer session through the Columbia Lighthouse Project. Those completing the training are certified to administer the C-SSRS, and will receive a training certificate. As the MINI will be used to establish subject initial eligibility with respect to suicidality, the "Since Last Visit" version of the C-SSRS interview will be conducted at the randomization visit prior to the first dose and then every 4 weeks ± 1 week thereafter through Week 64. The interview can be conducted by telephone at all scheduled times or in person at the clinic visit.. At Week 1, this scale will be used to assess current suicidal ideation since the MINI interview. This questionnaire will be administered by a clinical staff member and subject responses will be recorded either on a paper CRF or electronically into an eCRF. If an eCRF is used, it will serve as both the source and eCRF.

10. SAFETY MONITORING

10.1. Responsibilities for Ensuring the Safety of Study Participants

The national regulatory authority (Australian Therapeutic Goods Administration [TGA]), FDA (through virtue of this being an IND study and that US sites are also participating), the study sponsor, the institution through which the research is performed and all members of the PI's clinical team share responsibility for ensuring that the participants participating in this study are exposed to the least possible risk of AEs that may result from participation in this study. These responsibilities are defined in the Australian National Health and Medical Research Council (NHMRC) guideline "Safety monitoring and reporting in clinical trials involving therapeutic goods" (NHMRC 2016) and are itemized below and contained in the Study Safety plan (CNSWIPV001).

10.2. Principal Investigator

The PI has a personal responsibility to closely monitor study participants and an inherent authority to take whatever measures necessary to ensure their safety, including ensuring that procedures and expertise are available to cope with medical emergencies during the study. The PI has the authority to terminate, suspend or require changes to a clinical study for safety concerns and may delay an individual's IMP administration or pause study drug administration in the whole trial if he/she has concerns that the study drug may place a participant at significant risk. Investigators should assess all AEs and act on any AEs as clinical care dictates. The role of the investigator with regard to safety reporting is to provide the sponsor with all relevant information so that an appropriate safety analysis can be performed.

- Capture and assess all AEs that occur at the site as required and in accordance with the protocol.
- Report to the sponsor **within 24 hours of becoming aware of the SAE**:
    - All SAEs, except those that are identified in the protocol as not needing immediate reporting.
    - Any occurrences of congenital anomaly/birth defect arising from any pregnancy of a participant (or partner); and
    - All Urgent Safety Measures (USMs) instigated by the site.
- Report to the sponsor as specified in the protocol:
    - All safety critical events (see definitions in Section 10.11.1) and
    - Any additional requested information relating to reported deaths.
- Report to the institution **within 72 hours** of becoming aware of the event:
    - All significant safety issues
    - All Suspected Unexpected Serious Adverse Reactions (SUSARs) arising from the local site.

Only medically qualified investigators can assess an AE. Assessment of AE processes for handling consent for follow-up of participants (or pregnant partners of participants) are to be

documented in the Study Safety plan. SUSARs are to be reported to the investigator's institution when in the investigator's judgment, a SUSAR has occurred. The PI should not unblind the SUSAR for the purposes of reporting to their institution.

10.3. Study Pharmaceutical Sponsor

The sponsor also has an institutional responsibility to ensure participant safety and undertakes to promptly notify the concerned investigators, HREC/IRB, TGA and FDA of findings that could adversely affect the safety of participants included in the study, impact the conduct of the study, or alter the HREC/IRB approval/favorable opinion to continue the study. This includes the expedited reporting to these parties of all adverse drug reactions (ADRs) that are both serious and unexpected (SUSAR).

Under 21 CFR 312.50, sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described in 21 CFR 312.

Under 21 CFR 312 (c)(1) IND safety reports, the sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Specifically, the sponsor should:

- Ensure that the trial protocol has clear sections describing:
    - The assessment and management of risk (if not in an alternative document). The trial protocol and/or the safety monitoring plan, should describe the composition, roles and responsibilities of oversight committees and plans for ongoing safety monitoring;
    - Safety reporting definitions, procedures, responsibilities and reporting timelines; and
    - Any SAEs that do not require immediate reporting.
- Keep detailed records of all reported AEs and maintain up-to-date tabulations and/or line listings. The sponsor may be required to provide tabulations/line listings to the TGA and FDA on request.
- When communicating safety information to investigators and/or HREC/IRBs, clarify the impact of each report on patient safety, trial conduct or trial documentation
- Assess and categorise the safety reports received from investigators, and report all SUSARs occurring in participants to the TGA and FDA under IND 129,656 (in accordance with (IAW) 21 CFR 312.32):

- For fatal or life threatening SUSARs, immediately, but no later than **7 calendar days** after being made aware of the case, with any follow-up information within a further 8 calendar days.
- For all other SUSARs, no later than **15 calendar days** after being made aware of the case.

When determining whether a SUSAR has occurred, where the sponsor's causality assessment conflicts with the assessment made by the site investigator, the site investigator's assessment cannot be downgraded by the sponsor (i.e., altered from 'related' to 'not related'). In this case, if an investigator's judgment triggers the reporting of a SUSAR, the opinion of both the investigator and the sponsor should be provided with any SUSAR report sent to the TGA and the FDA.

When reporting a SUSAR to the TGA and FDA, the blind should generally be broken by the sponsor (See Section D of ICH guideline E2A Managing Blinded Therapy Cases). In order to avoid introducing biases, the blind should be maintained for all other persons involved in the conduct or management of the trial, including those responsible for data analysis and/or interpretation of results.

- Review the IB at least annually and update it when new and relevant information becomes available;
- Provide the HREC/IRB and investigators with any update/addenda of the IB;
- Provide the HREC/IRB with an **annual safety report (i.e., drug safety update report [DSUR)])** including a clear summary of the evolving safety profile of the trial. This report should allow the HREC/IRBs to assess whether ongoing safety monitoring is being conducted appropriately and that the trial's safety monitoring plans are being followed and where necessary, are being adapted to take into account new findings as the trial progresses.
- Ensure that all sponsor responsibilities for safety monitoring and reporting (e.g. reporting SUSARs and significant safety issues to the TGA and FDA) are appropriately allocated or delegated.
- Notify the TGA, FDA, HREC and investigators of all **significant safety issues** that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. Significant safety issues that meet the definition of a USM should be notified **within 72 hours**, and all other significant safety issues (SSI) should be notified **within 15 calendar days** of the sponsor instigating or being made aware of the issue. Examples include:
  - An SAE that could be associated with the trial procedures and that requires modification of the conduct of the trial;
  - A hazard to the patient population;
  - A major safety finding from a newly completed animal study (such as carcinogenicity);
  - A temporary halt/termination of a trial for safety reasons;
  - Recommendations of the DSMB where relevant for the safety of participants, such as an increase in frequency or severity of an expected ADR, single case

events (e.g., toxic epidermal necrolysis, agranulocytosis, hepatic failure) that lead to an USM.

Often, SSIs do not fall within the definition of a SUSAR and thus are not subject to the reporting requirements for SUSARs. Significant safety issues usually require other action, such as the reporting of an USM, an amendment, a temporary halt or an early termination of a trial. In addition, SSIs often result in safety-related changes to trial documentation. These amendments should be submitted to the HREC/IRB **without undue delay**.

Urgent safety measures are one type of SSI where sponsors or trial investigators act immediately to protect participants from an immediate hazard to their health and safety. Consequently, USMs are often instigated before the TGA, FDA and HREC/IRB are notified. In these cases, it is strongly recommended that the sponsor **contact the TGA within 24 hours** of the measure being taken.

If this initial contact is by telephone, it should be followed-up with a written notification provided by facsimile or e-mail within 72 hours. Table 4 illustrates the types of action that result from SSIs and the associated timelines for **written notification**.

Table 4: Sponsor Reporting of SSIs

Action	What is communicated	Recipients	Timelines and further review
USM	Reason Measures taken Further actions planned	TGA, FDA investigators, HREC/IRB	Without undue delay and NLT **72 hours** of the USM being taken
Notification of an amendment	Details of the SSI Further actions planned	TGA, FDA investigators, HREC/IRB	Without undue delay and NLT **15 calendar days** Sponsors should submit to the HREC/IRB an amendment relating to any revised trial documentation **without undue delay**
Temporary halt of a trial for safety reasons	Reasons Scope of halt (i.e., suspension of recruitment, or cessation/interruption of treatment)	TGA, FDA investigators, HREC/IRB	Without undue delay and NLT **15 calendar days** of Sponsor's decision to halt the trial Where necessary to seek HREC/IRB review of related actions (e.g., informing participants, or arranging continuing care/follow-up), a letter describing these actions should be submitted to the HREC/IRB within **15 calendar days** of the temporary halt

NLT=no later than; SSI=significant safety issue; USM=urgent safety measure.

10.4. Responsibilities of the Local Australian Sponsor

The local Australian sponsor will fulfill obligations documented in the master services agreement including:

- Maintain appropriate clinical trial insurance;

- Interact with the TGA including but not limited to signing regulatory submissions to be filed with the TGA on behalf of the sponsor;
- Communicate in a timely manner all written communications with the TGA to the sponsor;
- Provide services that compliance with the Master Services Agreement, Protocol, applicable requirements and guidelines of the TGA, and patient privacy laws and regulations (collectively, "**Laws**"), CPMP/ICH/135/95, World Medical Association Declaration of Helsinki (1996 version); National Statement on Ethical Conduct in Human Research (NHMRC 2007a, updated May 2015); CNS SOPs and any authorization for the trial issued by the TGA and the terms and conditions of the favorable opinion of the HREC.

10.5. Local Medical Monitors

LMMs, in consultation with the DSMB, will provide medical review during the execution of the study. This oversight will include the reviewing of safety information and the provision of applicable recommendations to both the investigator and the sponsor. This review is intended to facilitate the early detection of safety signals and to maximize the chances for the continued appropriateness of the study and the protection of the study participants.

LMMs will be responsible for the following safety monitoring:

- Reviewing the eligibility of potential participants in consultation with the investigators;
- Evaluation of study safety data on an ongoing basis to assess the relevance of findings to study stopping criteria;
- Evaluation of AEs, SAEs and corresponding safety reports (including the assessment of severity, causality and expectedness of events); and
- Providing reports of clinical and safety data to the DSMB.

Under HRPO guidelines the LMM (Research Monitor) may also:

- Observe recruitment and enrollment procedures and the consent process for individuals
- Oversee study interventions and interactions;
- Review monitoring plans and unanticipated problems involving risk to participants or others (Unanticipated Problems Involving Risks to Subjects or Others [UPIRTSO]) reports; and
- Oversee data matching, data collection and analysis.
- At a minimum, the LMM may discuss the research protocol with the investigators, interview human participants and consult with others outside of the study about the research.
- The LMM shall have authority to stop a research protocol in progress, remove individual human participants from a research protocol and take whatever steps are necessary to protect the safety and well-being of human participants until the HREC/IRB can assess the research monitor's report.

- The LMM shall have the responsibility to promptly report their observations and findings to the HREC/IRB, other designated official and the HRPO.

10.6. Responsibilities of the Institution

- Assess whether any safety reports received impact on medico-legal risk, the responsible conduct of research, adherence to contractual obligations or the trial's continued site authorisation and, where applicable, facilitate the implementation of corrective and preventative action.
- Develop clear guidance for investigators detailing the requirements for safety reporting and monitoring in clinical trials.

10.7. Responsibilities of the HREC/IRB

The sponsor, through their independent safety monitoring arrangements, has the primary responsibility for monitoring the ongoing safety of the IMP. The HREC/IRB should be satisfied that the sponsor's arrangements are sufficiently independent and commensurate with the risk, size and complexity of the trial. The approving HREC/IRB should:

- Assess the safety of proposed trials, including whether the evaluation of the anticipated benefits and risks is satisfactory and ensure that the sponsor has proportionate systems in place to mitigate and manage any identified risks.
- Satisfy itself that the sponsor's ongoing safety monitoring arrangements are adequate, including the justification for appointing/not appointing a DSMB and any 'stopping rules' or criteria for withdrawing individual participants from the trial.

10.8. Responsibilities of the TGA and FDA

The TGA or FDA may:

- Conduct an audit of a clinical trial where necessary on safety grounds; and
- Stop a trial where that action is in the public's interest.

10.9. Data and Safety Monitoring Board

An independent, suitably qualified DSMB will be convened and will meet quarterly during the study to review safety data during the conduct of the clinical investigation. The DSMB will include both an independent ophthalmologist (retinal specialist) and psychiatrist.

The DSMB will meet prior to the start of the study, quarterly during enrollment and follow-up and at trial end to review safety data. The Board will be responsible for recommendations related to the safety of participants and the continuation of the study. The Board will review SAEs for the duration of the trial and all pregnancies and evaluate any safety issues with respect to trial conduct. A separate DSMB charter will be drafted for the study. The Board will be blinded to participants' actual randomized group assignments but may request at any time that the blind be broken by the Data Management Site, if concerns arise from the blinded data. *Ad hoc* meetings will be convened if SAEs occur that are considered at least possibly related to the IMP.

10.10. Safety Surveillance During the Study

Participants will be monitored and safety data collected by way of clinical interviews, observations and examinations and laboratory evaluations. Time points and the specific data collected for each of these evaluations are described in Section 8 and Section 9.

Any signs and symptoms of ADRs to IMP will be treated symptomatically.

10.11. Adverse Events

The collection, evaluation and reporting of AEs/ADRs arising from this clinical study will be performed in accordance with:

- Detailed guidance on the collection, verification and presentation of AE/ADR reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01);
- ICH guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting; and
- ICH guideline E2F: Note for guidance on DSUR.

The definitions of AEs, ADRs, SAEs, and SUSARs are given below. It is of the utmost importance that all staff involved in the conduct of clinical research is familiar with the content of this section.

10.11.1. Definitions

An **adverse event (AE)** - any untoward medical occurrence in a patient or clinical trial participant administered an IMP and that does not necessarily have a causal relationship with the treatment.

An **adverse drug reaction (ADR)** – any untoward and unintended response to an IMP related to any dose administered. Any AE judged by either the reporting investigator or the sponsor as having a reasonable possibility of a causal relationship to an IMP would qualify as ADRs. The expression "reasonable causal relationship" means, there is evidence or argument to suggest a causal relationship.

The following are examples of types of evidence that would suggest a causal relationship between the IMP and the AE:

- A single occurrence of an AE that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an AE that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).
- An aggregate analysis of specific AEs observed in clinical trials (such as known consequences of the underlying disease or condition under investigation or other AEs that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in the a concurrent or historical control group.

An AE/ADR may be:

- A new symptom, sign or medical condition;

- A new diagnosis;
- An intercurrent illness or accident;
- An exacerbation of a pre-existing medical condition/disease;
- The recurrence of a disease;
- An increase in frequency or intensity of a pre-existing episodic disease or symptom;
- An abnormal assessment (e.g., change on physical examination) if it represents a clinically significant finding that was not present at study start or worsened during the course of the study; or
- An abnormal laboratory assessment or change in a laboratory parameter.

Borderline abnormal laboratory findings and other objective assessments should NOT be routinely captured and reported as AEs, as they will be collected and analyzed separately. However, abnormal laboratory findings or other objective measurements that meet the following criteria should be captured and reported in the AE section of the eCRF:

- The result meets the criteria for reporting as an SAE;
- The test result is associated with accompanying symptoms; and/or;
- It requires additional diagnostic testing or medical/surgical intervention; and/or;
- It leads to a change in trial dosing outside of protocol-stipulated dose adjustments, or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy; and/or
- It is considered by the investigator or sponsor to be clinically significant or represent a clinically significant change from baseline.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE/ADR. Any abnormal test result that is determined to be an error does not require reporting as an AE.

If a clinical diagnosis is associated with an abnormal laboratory finding, the relevant AE should be recorded as the diagnosis rather than the incidental laboratory finding (e.g. “hepatitis” should be recorded rather than “elevated transaminases”).

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions, which may, or may not, be AEs/ADRs. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs if the condition was present before inclusion in the trial. In the latter case the condition should be reported as medical history.

An ADR is regarded as an **unexpected adverse reaction** if its nature or severity is not consistent with the applicable reference safety information (Investigator’s Brochure). Events that add significant information on the specificity, severity or frequency of previously described reactions, are also regarded as unexpected.

The expectedness of an ADR is determined by the sponsor in the reference safety information and will be evaluated in the context of previously observed events, rather than on the basis of what might be anticipated from the pharmacological properties of a medicinal product.

For this protocol, the reference document is the 60P IB.

A **Serious Adverse Event/Reaction (SAE/SAR)** is defined as an event or reaction which:

- Results in death;
- Is life-threatening (the term "life-threatening" in the definition of "serious" refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe);
- Requires hospitalization or prolongs existing hospitalization, unless this is for:
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the trial and has not worsened since the start of the IMP;
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission;
    - Cosmetic surgery or for social reasons or respite care in the absence of any deterioration in the participant's general condition;
- Results in persistent or significant disability/incapacity;
- Is a congenital abnormality/birth defect;
- Is considered medically important (medical and scientific judgment should be exercised in deciding whether other AE/ADRs are to be considered serious, such as important medical events that may not be immediately life threatening but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; convulsions that do not result in hospitalization; development of drug dependency or drug abuse); and
- For the purpose of this protocol an AE will be considered as serious should the AE constitute a possible Hy's Law case (defined as a participant with any value of ALT or AST greater than or equal to 3x upper limit of normal (ULN) together with an increase in bilirubin to a value greater than 2x ULN (>35% direct) and NOT associated cholestasis (ALP value less than 2x ULN).

A **non-serious** AE/ADR is any symptom or sign, which does not fulfill any of the above-mentioned seriousness criteria.

A Safety Critical Adverse Event is any adverse event and/or laboratory abnormality identified in the protocol as critical to safety evaluations that should be reported to the sponsor according to the reporting requirements specified in the protocol.

A **Significant Safety Issue (SSI)** is any safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.

A **Suspected Unexpected Serious Adverse Reactions (SUSAR)** is any SAE where a causal relationship with the IMP is at least a reasonable possibility, but the event is not listed in the 60P IB.

An **Urgent Safety Measure (USM)** is any measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HREC/IRBs or Institutions.

An **Unanticipated Problem Involving Risk to Subjects or Others** (UPIRTSO) is defined as any problem or event which, in the opinion of the local investigator, was unanticipated, places participants or others at a greater risk of harm than was previously know or recognized, and was possibly related to the research procedure.

An **Adverse Events of Special Interest (AESIs)** for this study are defined as:

1. Hepatic:
    a. Possible Hy's law case: defined as a participant with any value of ALT or AST above 3x ULN together with an increase in bilirubin to a value higher than 2x ULN and not associated with cholestasis (ALP value less than 2x ULN) (to be reported as an SAE as detailed above);
    b. Any ALT or AST above 3x ULN;
    c. Any elevation in bilirubin 2x ULN;
    d. Any AST or ALT above 2x ULN and (total bilirubin [TBL] >1.5x ULN); and
    e. Any AST or ALT above 2x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (eosinophil percent or count above the ULN).
2. Ophthalmic:
    a. Functional change on microperimetry test showing an abnormality in the paracentral region forming a ring or partial ring.
    b. New abnormality by FM-100 hue test.
    c. Significant deterioration in the Mars letter contrast sensitivity test with a change exceeding 0.12 logCS.
    d. Unexplained marked reduction of visual acuity ≥15 letters that persists for ≥2 visits separated by at least one week.
    e. A ≥15 letter change [≥ 3 lines] change in ETDRS BCVA at 4 meters.
3. Hematologic
    a. Methemoglobin > 10%.
4. Other:
    a. Any other AE that, in the opinion of the investigator, is related to the IMP and may jeopardize the participant's safety.

Although not considered an AE, pregnancy in female participants will be reported as an **event of special interest** as per Section 10.11.6.

10.11.2. Assessment and Recording of Adverse Events

It is the investigator's responsibility to document and report all AEs occurring in the clinical trial whether spontaneously reported by the participant, observed by the investigator (either directly or by laboratory or other assessments), or elicited by general questioning.

The period of observation for collection of AEs extends from the time of dosing (Day 1, Week 1 [Visit 2]) through the Week 64 follow-up visit. Those participants meeting the criteria for additional safety follow-up (Section 8.5 will be followed every 3 months thereafter to a maximum of 12 months until the AE resolves or stabilizes.

SAEs will be reported from the time of screening until 30 days following the EOS visit (Week 64) (if spontaneously reported by the participant). Serious adverse events experienced

after this 30-day period will only be reported if the investigator suspects a causal relationship with the study drug.

The following information should be recorded for all AEs:

- The name of the AE;
- The dates of onset and resolution of the event;
- The characteristics of the event (seriousness, intensity);
- The action taken in response to the event (including treatment required);
- The outcome of the event; and
- The relationship of the event to the study drug (causality assessment) and/or to study participation.

Standard toxicity grading

The medical assessment of AE severity of the study will be recorded in accordance with the Common Terminology Criteria for Adverse Events v 4.03 that went into effect June 14, 2010 (CTCAE V4.03). Note however, if the local site's normal blood pressure ranges overlap with that considered to be a grade 1 toxicity according to the CTCAE, that the upper limit of the local sites scale will be considered the cutoff for reporting an AE.

- Grade 1: Mild - asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- Grade 2: Moderate - minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL);
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL;
- Grade 4: Life-threatening consequences; urgent intervention indicated.

Severity grading (AEs not included within CTCAE V4.03)

The medical assessment of AE intensity will be provided in the participant's eCRF. The maximum intensity of the event will be graded as per the following definitions:

- Mild – Does not interfere with participant's usual function;
- Moderate – Interferes to some extent with the participant's usual function; and
- Severe – Interferes significantly with participant's usual function.

Relationship to IMP

The investigator must assess the relationship of each event to the IMP and decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the IMP. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Alternatively, if there is any valid reason for suspecting a possible cause-and-effect relationship between the IMP and the occurrence of the AE (even if undetermined or untested), then the AE should be considered "related". This should be documented in the participant's source documentation and eCRF.

The following may guide this assessment:

- **Not related:** No relationship to investigational product. Applies to those events for which evidence exists that there is an alternate etiology.
- **Unlikely related:** Likely unrelated to the investigational product. Likely to be related to factors other than investigational product, but cannot be ruled out with certainty.
- **Possibly related:** An association between the event and the administration of investigational product cannot be ruled out. There is a reasonable temporal association, but there may also be an alternative etiology such as the participant's clinical status or underlying factors including other therapy.
- **Related:** An association exists between the receipt of investigational product and the event. An association to other factors has been ruled out.

Where possible, a distinction should be made between events considered related to the IMP and those related to protocol-mandated procedures.

In addition to the assessment of IMP relationship, the investigator should comment on the AE record in the eCRF whether an AE is considered related to the participation of the participant (study procedures etc.).

Outcome

The investigator will follow up all AEs wherever possible until they have resolved or stabilized.

The date of confirmation of the outcome will be recorded and the course of the AE will be assessed in accordance with the following classification:

- Recovered: The AE has resolved and the participant returned to their condition prior to onset;
- Recovered with sequelae: The AE resolved, but the participant has sequelae;
- Recovering: The AE has almost resolved and the participant is returning to his condition prior to onset;
- Death: The participant died; causal relationship is not object;
- Ongoing: The AE had not resolved and the participant's condition remained unchanged at the last time of observation. In case of death from a different cause, events ongoing at the time of death will be classified as such; and
- Unknown.

10.11.3. Action taken and follow-up of events

All AEs must be documented and followed up by the investigator **until:**

- The event is resolved; or
- No further medically relevant information in relation to the event can be expected; and
- The investigator considers it justifiable to terminate the follow-up.

Events that are unresolved at the time of the participant's last follow-up visit should continue to be followed up by the investigator for as long as medically indicated (up to 12 months).

The sponsor retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

All AEs should be treated appropriately. The investigator will decide upon the appropriate action to be taken in response to an AE, which may include one or more of the following:

- No action taken (i.e. further observation only);
- Dosing with the IMP is withheld and the participant withdrawn from the study;
- Administration of a concomitant medication;
- Hospitalization or prolongation of current hospitalization (event to be reported as an SAE); and
- Other.

10.11.4. Reporting of SAEs

The investigator will take immediate appropriate action in response to SAEs to ensure participant safety and in an attempt to identify the causes of the event. The investigator will notify the LMM, the CNS Project Manager (Australian Site), Fast-Track's Project Manager (US sites) and the sponsor's Chief Medical Officer of the occurrence of any SAE within 1 business day of becoming aware of the event. The notification should be in writing by email or fax and documented on a standard SAE reporting form. Reporting to the local HREC/IRB should follow their policies. In addition to this, fatal or life-threatening SAEs that the investigator suspects are related to **the IMP should be reported by telephone to the LMM as soon as possible upon the investigator becoming aware of the event.**

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CNS Project Manager:
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Local US Medical Monitor:
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Fast-Track Drugs & Biologics, LLC Project Manager
Katrina Riggs, CCRA
Email: kriggs@fasttrackresearch.com
Phone: +1 301-762-2609

IntegReview IRB:
Email: integreview@integreview.com
Telephone: 512-326-3001

Sponsor's Chief Medical Officer:
Bryan Smith, MD, FAAFP
Email: bryansmith@60degreespharma.com
Phone: +1 (301) 807-8548

The initial report will be followed up by a full written report within 3 business days or 5 calendar days, whichever comes first unless no further information is available when the follow-up report will be provided as soon as possible when new information becomes available. Further follow-up reports will be provided as and when new information becomes available. Photocopies of results, consultant report(s), a summary of the outcome of the reaction and the investigator's opinion of IMP relationship to the SAE will accompany the SAE form if and when available.

In addition to the assessments provided by the investigator, the sponsor will also perform an evaluation of the seriousness, causality and expectedness of all SAEs. All SAEs judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an IMP will qualify as serious ADR. If the sponsor disagrees with the investigator's causality assessment, both the opinion of the investigator and the sponsor will be documented in the safety report.

The LMM will notify the sponsor and all members of the DSMB of any reported SAE within 24 hours of becoming aware of the event and will continue to provide all follow-up information in a timely manner.

All SAEs will be included in the main study database.

The TGA, FDA and HREC/IRB will be notified of all SUSARs within 7 days (for fatal and life-threatening SUSARs) or 15 days (all other SUSARs) of receipt of the event report.

Submissions to TGA should be made using a Council for International Organizations of Medical Sciences (CIOMS) form to adr.reports@tga.gov.au or via the TGA Business Services (TBS) ADR submission portal. E2B reports should be emailed to adr.reports@tga.gov.au. For further information on SUSAR reporting to TGA, email: adr.reports@tga.gov.au or call +61 1800 010 624. SUSAR submissions to the FDA will be via MedWatch reporting.

CNS will work with Fast-Track to submit SUSAR reports to both TGA and FDA (as per the transfer of obligations form submitted under IND 129,656).

The investigator will be responsible for notification of the HREC/IRB.

Annual safety reporting to the national Competent Authority and the Ethics Committee will be in agreement with ICH guideline E2F "Note for guidance on development safety update reports (DSUR) and the NHMRC guideline "Safety monitoring and reporting in clinical trials

involving therapeutic goods (NHMRC 2016). The DSUR compilation responsibilities will be described in the safety monitoring manual.

In addition, any other safety issue, which may alter the current benefit–risk assessment of the IMP, will be reported by the sponsor (or delegate) on an expedited basis to Health Authorities, HREC/IRB and the investigator.

Only UPIRTSOs will be reported to HRPO as per the safety manual. All UPIRTSOs will be reported to DVC and HRPO within a 7-day SUSAR reporting window.

USAMRMC Office of Research Protects Contact:
US Army Medical Research and Materiel Command
ATTN: MCMR-RPI
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Tel: +1 (301) 619 6240
Email: usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil

10.11.5. Reporting of AESIs

All AESIs (defined in Section 10.11.1) including those that do not meet the definition of an SAE, must be reported to the LMM and the CNS/Fast-Track Project Manager (with the sponsor Chief Scientific Officer on copy) within 24 hours of the investigator becoming aware of the occurrence of the AESI.

10.11.6. Reporting of Pregnancy

Pregnancy in a female participant during the study should be reported and followed as described below. Pregnancy does not constitute an AE as such and the pregnancy outcome will not be recorded in the eCRF unless it is considered to be an AE.

Pregnancies will lead to discontinuation of IMP administration and the participant will be followed up until Week 76.

The investigator must notify the LMM, the CNS/Fast/Track Project Manager and the Bellberry HREC/IRB in an expedited manner of any pregnancy occurring from the date of informed consent signature until 12 weeks after administration of tafenoquine. The HRPO will not be informed of pregnancy events. Part I of the Pregnancy Report Form (CNSSOPPV002 form or US Equivalent form) should be used for this notification, which should follow the same procedures and timelines, described for expedited AE reporting in Section 10.11. In all cases, the pregnancy must be followed until birth of the child, and the outcome of the pregnancy and birth reported as above by completing Part II of the Pregnancy Report Form (CNSSOPPV002 form or US Equivalent form) used for the initial notification. The timelines of the outcome reporting vary as follows:

- Normal outcomes should be reported within 45 days of birth/delivery; and
- Abnormal outcomes should be reported in an expedited manner as described in Section 10.11. An additional SAE Report form must be completed if the participant or participants' partner sustains a serious event, while a patient clinical/fetus report (PCFR) must be completed should the child/fetus sustain an event.

11. DATA MANAGEMENT

11.1. Data Collection

The investigator will maintain source documents for each participant in the study. Information entered into eCRF will be traceable to these source documents in the participant's file. The investigator must certify that the data entered into the eCRF are complete and accurate.

After database lock, the investigator will retain copies of the participant data for archiving at the study site.

11.2. Site Monitoring

During the study, appointed study monitors will visit the site regularly to check the completeness of participant records, the accuracy of entries in the eCRF, adherence to the protocol and to ICH GCP, the progress of enrolment, and to ensure that the IMPs are being stored, dispensed, and accounted for according to the prescribed conditions. Key study personnel must be available to assist the study monitor during these visits.

The investigator must allow the study monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Verification of 100% of source data will be performed. No information in source documents regarding the identity of the participants will be disclosed.

11.3. Database Management and Quality Control

Data management, including the development and management of a secure database, will be performed in accordance with the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Module (SDTM) requirements. The Data Management Site will review the data entered into the eCRF by investigational staff for completeness and accuracy. A formal querying process will be followed whereby the Data Management Site will work with CNS's clinical monitors to post queries to the EDMS for site personnel clarification of any apparent erroneous entries or inconsistencies and will request additional information from the site as required.

Primary source document for this study will be the participant's research record. The source documents will be retained at the site.

For this study, an EDMS will be used for the collection of the study data in an electronic format. The EDMS will be designed based on the protocol requirements, the approved eCRF layouts and specifications, and in accordance with 21 CFR Part 11. The eCRF layouts and specifications define and identify the applicable source data that will be collected and captured into the EDMS. The applicable source data will be electronically transcribed by the site designee onto the eCRF (data entry screens) in the EDMS. The investigator is ultimately responsible for the accuracy of the data entered into eCRF. Data monitoring and management will be performed in the EDMS by the study clinical monitor and the designated Data Management Site.

In addition to eCRF data, electronic transfer of data from the Blinded Reading Site, responsible for SD-OCT, qFAF, and color photos evaluations of both eyes evaluations will be performed periodically during the study.

A detailed data management plan will be written by the Data Management Site and approved by the sponsor's representative prior to study start. All updates to the data management plan must be approved before study closeout and database lock.

Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology (version 20.0 or later). Concomitant medication will be coded according to the WHO-Drug Dictionary Enhanced (DDE).

After all data have been captured and reviewed, all queries have been resolved with the site and any protocol non-compliances that were identified during the data management processes have been confirmed by the site, the database will be declared to be complete and accurate, it will be locked and made available for data analysis. All blinded personnel may be unblinded at this time. Any changes to the database after that time may only be made by the data manager, in consultation with the sponsor and in accordance with documented database unlock and relock procedures.

12. STATISTICAL METHODS

The following sections describe the statistical analysis as it is foreseen when the study is being planned. A detailed SAP will be finalized and approved and will provide details of all analyses to be performed as well as the format of listings and tables to be provided for completion of the FCSR. Any deviations from the SAP will be described and justified in the FCSR.

12.1. Sample Size Calculation

The sample size estimate is based on the assumed SOSE (serious ophthalmic safety event) rate, as assessed by using SD-OCT and qFAF. Based on the binomial distribution, if the true SOSE rate is 1% in the tafenoquine group, there is a 95% probability to observe at least one SOSE with 300 participants.

This study could also be viewed as a non-inferiority safety study. The incidence of retinal abnormalities was conservatively assumed to be 1% (i.e., 99% without SOSE) for both placebo and tafenoquine group. For the primary endpoint, the specific ophthalmic abnormalities of interest that are not present at baseline are defined in Table 5. For secondary ophthalmic endpoints, the abnormality may be a new change in ophthalmic parameter when not present at baseline that arises concurrent to IMP therapy or a worsening of a pre-existing abnormality present at baseline concurrent to IMP therapy.

A non-inferiority margin of 2.5% (treatment-placebo, in terms of SOSE rates) was considered to be clinically relevant, and therefore used to compare the non-inferiority between tafenoquine and placebo. The 2.5% non-inferiority margin is estimated from literature. On an Australian population scale, the prevalence of maculopathy is 1.3% in age cohorts 49-54 years with increasing prevalence in cohorts aged 55-64 (2.6%), 65-74 (8.5%), 75-84 (15.5%), and 85+ (28.0%) years (Mitchell 1995). The 2.5% NI margin sets a lenient threshold to determine if tafenoquine causes retinal deficits beyond what is expected even in a high-risk group at the upper age range of 55 years for the study population. That is, if the SOSE rate for tafenoquine group is not more than 2.5% higher than the placebo, the safety for tafenoquine will be regarded as no worse than placebo. For a two-sided significance level of 5% (α=0.025 one-sided) with 600 randomized subjects, the power is 86% (β=0.14) to test the NI margin.

Analysis Sets

Safety population: All participants who received study treatment at least once will be included in the safety population. This is the primary population for safety and tolerability analysis.

Intention-to-Treat (ITT) population: The ITT population will consist of all participants as they are randomized to the study. Primary and secondary ophthalmic endpoints will be analyzed by ITT population. In this non-inferiority setting, analysis based on ITT population provides supportive evidence to analyses based on Per Protocol population.

Per Protocol (PP) population: All participants who received at least 25% of the total planned dose for IMP, had at least one valid baseline and post baseline evaluations by SD-OCT and qFAF, and had no major protocol deviations will be included in the PP population. This is the primary population for the primary safety endpoint analysis and other secondary ophthalmic endpoints.

Though this is a safety study, all subjects will be analyzed as randomized in all the above study populations.

12.2. Analysis and Presentation of Data

12.2.1. General

Detailed aspects of the analysis will be presented in the SAP which will be finalized prior to unblinding.

In general, for safety analyses, descriptive statistics will be tabulated by treatment group for all participants. Unless otherwise stated, all safety analyses will use the Safety Analysis population. The analysis of AEs will consider only treatment emergent AEs (TEAEs), events occurring for the first time, or worsening, during or after the first administration of IMP. The analysis will focus on participant incidence, although for TEAEs of special interest, the number of events will also be provided (i.e., ophthalmic assessments). Tables summarizing TEAEs will be displayed by preferred term and SOC. Analysis of SAEs and the categorization of AEs by severity and relationship to IMP will also be included. AEs leading to study withdrawal or deaths on-study will also be analyzed in tables and/or listings.

Treatment-emergent changes in vital signs and laboratory parameters will be presented using tabulations by group. Descriptive statistics for each parameter and/or the change from baseline at each time point will be provided. Shift tables for selected laboratory endpoints will be presented (ALT, AST, total bilrubin, hemoglobin and methemoglobin) as defined in the SAP. For endpoints measured on a categorical scale the number of participants and proportions will be provided.

Missing data will not be imputed in general, unless otherwise specified. This is a safety study, thus multiplicity adjustment related to the primary and secondary safety endpoints analyses will not be considered.

12.2.2. Subject Demographics and Baseline Characteristics

The participant disposition and demographic data (including age, weight, height and race/ethnicity) will be tabulated by group and overall for both treatment groups. Study completion, study withdrawals, exclusions and violations will be listed and the reasons for withdrawal, exclusions and violations will be listed.

Data for background and demographic variables will be listed by treatment group and participant. Descriptive statistics will be provided by treatment group.

Medical, surgical and social history, current medical conditions results of laboratory screening tests, drug tests and any other relevant baseline information (including serology results, alcohol breathalyzer test, urine drug screen, and G6PD testing and pregnancy test results) will be listed by treatment group and participant.

Previous and concomitant medication taken at any stage from 4 weeks prior to dosing and during the study period will be listed per treatment group.

12.2.3. Safety Data

All treatment emergent AE data will be summarized separately by treatment group and by MedDRA SOC, MedDRA preferred term (PT) and severity and relationship of each AE observed.

Vital signs and routine safety laboratory data of potential clinical concern (outside local laboratory normal limits) will be summarized descriptively by treatment and time point. Both absolute values and change from baseline will be presented.

Shift tables (from the local laboratory reference range) will be generated for each treatment group to show out of range changes in laboratory parameters during the Treatment Phase.

Vital signs will be tabulated by treatment group.

The QT interval corrected for heart rate will be calculated using the Fridericia formula (QTcF) (Fridericia 1920). ECG interval data (PR, QRS, (QTcF) will be presented as summary statistics. The numbers and percentages of subjects with QTcF > 450 msec and those with clinically significant findings will be presented in a table.

Investigational medicinal product dosing and exposure over time will be summarized by treatment group and provided in a listing for each participant.

12.2.3.1. Primary Endpoint

The primary endpoint is the proportion of participants with protocol-defined SOSE. SOSE is assessed by significant retinal changes from baseline using SD-OCT and qFAF. The details of significant protocol defined retinal changes using SD-OCT and qFAF are defined Table 5.

A detailed list of SD-OCT and qFAF parameters assessed in this study is presented in Appendix 1 and Appendix 2. Clinically significant changes for quantitative measures will be defined as a change from baseline by a threshold taken from previously published coefficient of repeatability (Table 5). For qualitative assessments, new findings or worsening of findings from baseline exams regarded to be of clinical importance by the Blinded Reading Site will be considered a change from baseline. If either of the automated reading (CST or TMV) is missing or deemed unreliable by the Blinded Reading Site; the parafoveal (inner ring of the ETDRS grid; the annular zone between foveal centered 1 mm diameter circle and 3 mm diameter circle) retinal thickness will be used to impute the missing data.

A descriptive summary table will be produced showing the results by each eye and across both eyes, for each assessment (including follow-up). The actual SD-OCT image of each eye will be included in the eCRF. Data from repeated tests carried out due to abnormal values will not be tabulated. All data, including those from repeat tests, will be provided in a listing.

For this primary endpoint, a participant will be considered to have a clinically significant SOSE if any of the five parameters listed below indicates a change from baseline in either eye at any time point during treatment. The 95% CI of SOSE rate will be calculated by treatment group, using the Clopper Pearson Exact methodology for the proportion of participants who did experience a clinically significant deterioration. The risk difference of the SOSE rates between tafenoquine and placebo will be estimated. The upper limit of two-sided 95% CI for the risk difference will be compared against the protocol pre-specified NI margin.

Table 5: Primary Endpoint Evaluation Criteria

Parameter	Result (change from baseline)	Criteria for Clinically Significant Change from Baseline[a]
SD-OCT CST[b]	Yes/No	Yes = change from baseline of at least 40 µm (15% change)
SD-OCT TMV[c]	Yes/No	Yes = change of ≥ 10% (0.86 mm^3) from baseline
SD-OCT parafoveal (inner ring of ETDRS grid) retinal thickness	Yes/No	Yes = change from baseline of at least 10 µm
SD-OCT ellipsoid and interdigitating zone disruption	Yes/No	Manual reading; Yes = any ellipsoid or interdigitating zone disruption (within the ETDRS grid) Graded as: Foveal (central subfield) Parafoveal (inner or outer ring) Extra macular (none in grid)
Abnormal quantitative auto fluorescence (qFAF) patterns	Yes/No	Manual reading: Yes = change in mid-ring $qFAF_8$ unit from baseline of at least 12%

[a] Note that these evaluations will be performed by the local site principal ophthalmologist.
[b] CST=central subfield thickness
[c] TMV=total macular volume

12.2.3.2. Secondary Endpoints

The incidence of AEs, SAEs, laboratory parameters and vital signs will be summarized descriptively by treatment group and study visit. The AEs will be summarized at ≥1% (common) and ≥10% (very common) level.

For the secondary safety endpoints, the proportion of participants with an abnormal change or new abnormal change will be compared by a Fisher's exact test between tafenoquine and placebo. The 95% CI of the abnormality rate will be summarized by Clopper Pearson Exact methodology. A logistic regression will be used to compare the risk of having the abnormality (odds ratio and 95% CI) between tafenoquine and placebo. These analysis methods will be applied to the following secondary safety endpoints: proportion of participants with abnormal changes from baseline observed on qFAF, proportion of participants with corneal deposits from slit lamp examination of the corneal epithelium, proportion of participants with new abnormal changes from baseline observed with color retinal digital photography (conventional and wide field), proportion of participants with new abnormal changes from baseline observed with microperimetry, proportion of participants with any new anomaly on the backlit ETDRS chart, proportion of participants with any clinically significant change in ETDRS BCVA (defined as ≥15 letter change [≥ 3 lines] of change in ETDRS BCVA at 4 meters), proportion of participants who develop a new color deficiency using the FM-100 hue test, proportion of participants who develop a loss of 0.12 or greater logCS on the Mars letter contrast sensitivity test, proportion of participants who develop a new identified psychiatric disorder, and proportion of participants with an AE of dizziness or vertigo and severity as assessed by the DHI.

For time to event safety endpoint, a log-rank test will be used to compare the time to onset/resolution of the event between tafenoquine and placebo. Cox regression will be used to compare the risk of having the safety endpoint (hazard ratio and 95% CI) between tafenoquine and placebo. The survival analysis methods will be applied to the endpoints of time to onset, and time to resolution of corneal deposits after treatment cessation.

Change from baseline in BCVA, key SD-OCT continuous parameters, and LSEQ component scores will be analyzed by a random intercept mixed model to account for correlation between repeated measures. Treatment effect (difference and 95% CI) on the change from baseline variables will be estimated across study visits.

Specifically, the following assessments will be conducted for secondary safety endpoints, and the extra analyses, if mentioned as below, will be applied.

- Mean change from baseline in key SD-OCT parameters including CST, TMV volume, and parafoveal (inner ring of ETDRS grid) retinal thickness and the proportion of participants with ellipsoid or interdigitating zone disruption. The difference in the proportion of participants with clinically significant ophthalmologic changes (as defined in the primary endpoint) between treatment group and the placebo group will be calculated. In addition, the change from baseline in individual SD-OCT and qFAF parameters listed in Appendix 1 and Appendix 2 will be tabulated and compared between tafenoquine and placebo-treated groups.
- Proportion of participants with abnormal changes from baseline observed on qFAF using the Spectralis HRA+OCT device with grey scale values extracted from these images for statistical analysis using qFAF software (Heidelberg Engineering).
- Mean change from baseline in BCVA. Changes from baseline in BCVA results by the ETDRS chart will be tabulated and compared between the two groups. A clinically significant deterioration is defined as a reduction of more than 4 letters from baseline (Week 1, Day 1 [Visit 2]) of 0.08 logMAR. The M-chart will be used to quantify the severity of the distortion (if detected). An additional analysis of BCVA changes will include the proportion of participants experiencing a 1-4 letter change (less than one line of ETDRS visual acuity change), a 5-9 letter change (1 line, but less than 2-line change), 10-14 letter change (2 lines, less than 3 lines) or 15 or more letter change (3 lines or more) in BCVA from baseline. A $\geq$15 letter ($\geq$ 3 line) or more change in ETDRS BCVA at 4 meters is considered clinically significant.
- Proportion of participants with corneal deposits from slit lamp examination of the corneal epithelium. Severity of corneal deposits by impairment of vision: The proportion of participants with grades I to IV keratopathy (Orlando grading system for cornea Verticillata, a specific pattern of corneal deposits. For participants with corneal deposits identified from slit lamp examination, the time to first onset and time to resolution after treatment cessation will be tabulated. Corneal structural changes are defined as changes from Baseline (Week 1, Day 1 [Visit 2]) of two or more grades of corneal changes. These data will also be provided in a listing.
- Time to onset of corneal deposits and overall time duration to resolution post treatment start.
- Time duration to resolution of corneal deposits after treatment cessation.

- Proportion of participants with new abnormalities compared with baseline observed with color retinal digital photography (conventional and wide field);
- Proportion of participants with new abnormalities compared with baseline observed with microperimetry;
- Proportion of participants with any new anomaly on the backlit ETDRS chart;
- Proportion of participants who develop a new color deficiency using FM-100 hue test;
- Proportion of participants who develop a loss of 0.12 or greater logCS on the Mars letter contrast sensitivity test;
- Retinal changes (structural) and the impact on macular function (functional) will be tabulated for each time point for each eye. The macular function tests include BCVA (ETDRS), Color vision assessment with FM-100 hue test, M-chart, and microperimetry. Clinically significant changes in any of the five tests are will be counted as having an impact on macular function. Retinal abnormalities on fundoscopy, digital fundus photography (conventional and wide field), SD-OCT and qFAF at Screening are considered to be structural changes but may not affect macular function with 12 months of treatment with tafenoquine.
- The proportion of participants with retinal abnormalities identified from digital photographs will be tabulated for each time point and overall. These data will also be provided in a listing;
- Proportion of participants who develop a new, current psychiatric disorder in accordance with the DSM-5 as assessed with the M.I.N.I 7.0.2 assessment questionnaire and suicidal ideation or suicide attempt by C-SSRS interview;
- Proportion of participants with a TEAE of dizziness or vertigo and severity as assessed by the DHI; and
- Mean change from baseline in GTS, QOS, AFS, and BFW as assessed by the LSEQ.

Grading of tafenoquine induced corneal deposits (cornea Verticillata):

The severity of cornea Verticillata (vortex pattern of benign corneal deposit) detected on slit-lamp microscopy will be classified according to the grading system for amiodarone-induced cornea Verticillata proposed by Orlando 1984. Amiodarone and hydroxychloroquine are both cationic amphiphilic drugs which induces phospholipidosis in the form of corneal deposits similar to tafenoquine.

Grade I: punctate opacities that coalesce to form a horizontal line in the inferior third of the cornea. This earliest sign is characterized by golden-brown micro deposits in the epithelium just anterior to the Bowman's membrane. These appear as a "dusting" of the cornea at the inferior pupillary margin in the mid periphery. There is no fluorescein epithelial punctate staining, foreign body sensation or other ocular symptoms.

Grade II: additional branching or arborization, resembling cat's whiskers. In this stage, the deposits become aligned in a more linear pattern and extend from the inferior pupillary margin towards the limbus. This give the appearance much like that of a "cat's whisker. There is a clear zone between the margin of the deposits and the limbus.

Grade III: the branches increase to assume a verticillate or whorl-like pattern. Linear "filament-like" deposits seen in grade II Verticillata increase in number and extend as

branches from the inferior pupillary area into the visual axis. A whorled pattern is seen in the pupillary axis of the cornea.

Grade IV: irregular clumps of pigment accompanying the whorled opacities. From grade III Verticillata, irregularly round “clumps” of golden-brown deposits can develop defining grade IV verticilla.

13. ETHICAL CONSIDERATIONS

13.1. Ethical Principles

The study will be conducted in accordance with:

- The most recent version of the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants;
- National Statement on Ethical Conduct in Human Research (NHMRC 2007a, updated May 2015);
- Notes for Guidance on Good Clinical Practice – Annotated with Comments (CPMP/ICH/135/95), as adopted by the Australian TGA (July 2000); and
- The current Clinical Trial Protocol as approved by the HREC/IRB and the USAMRMC HRPO.

The PI will take care to minimize any discomfort experienced by participants during the study. The only invasive procedures the blood collection by cannulation/venipuncture. The maximum amount of blood to be collected from an individual over the entire study period is approximately 135 mL (Appendix 3).

Additional blood samples may be taken for safety assessments as required by the PI or at times specified by the sponsor provided the total volume taken during the study does not exceed 140 mL during the study period.

13.2. Ethical Review

The protocol, consent forms and participant information sheets will be reviewed by the Bellberry-HREC, US IRB and HRPO. No study activities will be initiated prior to the approval of these documents by these committees. All amendments and addenda to the protocol will similarly be submitted to the Bellberry-HREC, IRB and HRPO for approval prior to their implementation.

13.3. Informed Consent Procedures

Participants will be fully informed of the nature of the study, the properties and side effects of the IMP and all relevant aspects of study procedures in the participant information sheet and informed consent document. The nature of the study, the IMP and its side effects will also be discussed with the participants by the investigator during recruitment. The participants may ask questions of the investigator or the clinic staff at any time.

The ‘Informed Consent’ form will be signed and dated by the participants in the presence of an investigator. Participants will also be given a copy of their signed ‘Informed Consent’ form.

In the event that the sponsor wants to perform testing on the samples that is not described in this protocol, additional HREC/IRB approval will be sought.

13.4. Subject Data Protection

Participants will be informed that their data will be held on file by the Study Site and that these data may be viewed by staff of the Australian Local Sponsor who are responsible for monitoring the study according to ICH GCP and by the local US FDA.

Upon request, the investigator(s)/institution(s) will permit direct access to source data/documents for trial-related monitoring, audits, HREC/IRB and HRPO review, and regulatory inspection(s) by the sponsor (or their appropriately qualified delegates) and Regulatory Authorities. Direct access includes examination, analysis, verification and reproduction of records and reports that are important to the evaluation of the trial.

They will similarly be informed that a report of the study will be submitted to the sponsor company and may also be submitted to government agencies in Australia and overseas and perhaps for publication, but that they will only be identified in such reports by their study identification number, initials and perhaps their gender and age. The investigators undertake to hold all personal information in confidence.

14. ADMINISTRATIVE CONSIDERATIONS

14.1. Liability/Indemnity/Insurance

The study sponsor will ensure sufficient insurance is available to enable it to indemnify and hold the investigator(s) and relevant staff as well as any hospital, institution, HREC/IRB or the like, harmless from any claims for damages for unexpected injuries, including death, that may be caused by the participant's participation in the study but only to the extent that the claim is not caused by the fault or negligence of the participants or investigator(s). The sponsor adheres to the guidelines of Medicines Australia for injury resulting from participation in a company-sponsored trial, including the provision of "no-fault clinical trial insurance" (Medicines Australia 2016).

14.2. Changes to the Final Study Protocol

Changes to the final study protocol can only be made with the prior consent of the sponsor and the HREC/IRB/HRPO. All such changes must be attached to, or incorporated into, the final protocol, and communicated to all relevant members of the Study Site staff and, if appropriate, to trial participants. All deviations from this study protocol will be reported on eCRFs and will be included in the trial master file and included in the FCSR. An assessment of the significance of each protocol deviation will be given in the FCSR. All deviations/amendments will be reported to sponsor.

14.2.1. Non-Substantial Amendment

Administrative or logistical minor changes to the protocol require a non-substantial amendment. Such changes include but are not limited to changes in study staff or contact details (e.g., sponsor instead of CRO monitors) or minor changes in the packaging or labeling of the IMP. An amendment deemed to be non-substantial must have no ethical implications.

The implementation of a non-substantial amendment may be done without notification to HRPO. However, the HREC/IRB will receive notification of non-substantial amendments.

14.2.2. Substantial Amendment

Significant changes to the protocol require a substantial amendment. Significant changes include but are not limited to: new data affecting the safety of participants, change to the objectives/endpoints of the study, the eligibility criteria, dose regimen, study assessments/procedures, treatment or study duration, with or without the need to modify the participant information sheet and informed consent.

Substantial amendments are to be approved by the HREC/IRB/HRPO. For HRPO purposes, substantial amendments may also include a change in the PI, change or addition of an institution, change to the HREC/IRB of Record, elimination or alteration of the consent process, change to the study that has regulatory implications, significant changes in the study design that would prompt additional scientific review or a change that could potentially increase risk to participants. The implementation of a substantial amendment can only occur after formal approval by the HREC/IRB /HRPO and must be signed by the PI.

14.2.3. Urgent Amendment

An urgent amendment might become necessary to preserve the safety of the participants enrolled in the study. The requirements for approval should in no way prevent any immediate action being taken by the investigators or the sponsor that is in the best interests of the participants. Therefore, if deemed necessary, an investigator can implement an immediate change to the protocol for safety reasons. This means that, exceptionally, the implementation of urgent amendments will occur before submission to and approval by the HREC/IRB /HRPO.

In such cases, the investigator must notify the sponsor within 24 hours of implementation of the amendment. A related substantial amendment will be written within 10 working days and submitted to the HREC/IRB /HRPO, together with a description of the steps, which have already been taken regarding implementation of this amendment.

14.2.4. Clinical Data Recording

Each participant will have a clinical file (source data) and eCRF, (for protocol specific data) into which relevant data will be recorded. A log of names, signatures and initials of all staff authorized to enter data into a participant's Clinic File and eCRF will be kept in the site study file.

Upon completion of each study visit, all eCRF data will be reviewed internally by the Study Site for omissions or apparent errors so that these can be corrected without delay. Any corrections made after the review and signature of the PI will be noted in the audit trail and will require re-authorization (electronic sign off) by the PI.

All deviations from this study protocol will be documented in the trial master file and included in the FCSR. An assessment of the significance of each protocol deviation will be discussed in the FCSR.

14.3. Record Retention

All source data, clinical records and laboratory data relating to the study will be retained in the archive of the Study Site for a minimum of 15 years after the completion of the study in compliance with TGA annotations to CPMP/ICH/135/95. Data will be available for retrospective review or audit by arrangement with the Chief Executive Officer of the Study Site. Written agreement from the sponsor must precede destruction of the same.

14.4. Biological Samples

Biological samples will be retained for the time required for assessment for analysis, and may then be discarded.

14.5. Shipment Procedures

The site staff will be responsible for shipment of samples to the sponsor nominated bioanalytical laboratories for testing. All samples will be securely packed in containers provided by the shipping vendor. These will be shipped as per the procedures of the vendor together with completed shipment forms.

14.6. Monitoring

It is the sponsor's responsibility to ensure that the study is monitored in accordance with the requirements of ICH GCP. The conduct of the study will be reviewed internally by the Study Site in accordance with the Study Site SOPs and ICH GCP guidelines. The trial will be monitored according to the sponsor's SOPs and all significant protocol deviations shall be reported to the sponsor and Bellberry HREC/IRB/HRPO using CNS or Fast-Track SOPS.

14.7. Reporting and Communication of Results

The data management, statistical and medical writing team appointed by the sponsor will collaborate to provide a detailed FCSR upon conclusion of the study. This will include appendices of all Tables, Listings and Figures generated during the analyses of data. The sponsor undertakes to ensure that all safety observations made during the conduct of the trial are documented in this report.

Publication and reporting of results and outcomes of this trial will be accurate and honest, undertaken with integrity and transparency and in accordance with the relevant clauses outlined in the Agreement between the clinical sites and Fast-Track. All manuscripts will need to be reviewed and approved by USAMMDA and 60P before submission. The sponsor recognizes that the PI has a responsibility to ensure that results of scientific interest arising from the clinical trial are appropriately published and disseminated. Publication of results will be presented to fair peer-review. Authorship will be given to all persons providing significant input into the conception, design, and execution or reporting of the research according to NHMRC guidelines (NHMRC 2007b). No person who is an author, consistent with this definition, will be excluded as an author without his/her permission in writing. Authorship will be discussed between researchers prior to study commencement (or as soon as possible thereafter) and reviewed whenever there are changes in participation. Acknowledgment will be given to the study participants and staff, and collaborating institutions and hospitals and other individuals and organizations providing finance or facilities. In any press releases, publications or presentations, the sponsor's financial contribution to the study and its participation in the collaboration and the trial site, shall be expressly acknowledged. The sponsor agrees that the Linear Clinical Research, in particular the PI, will be entitled to access all the de-identified clinical trial data upon completion of the study. Data will not be released publicly until the manuscript is accepted for publication. In the case of no publication, information will only be released to the public and media in accordance with the Linear Clinical Research's corporate media strategy policy.

As the IND holder and sponsor, 60P will register the trial on the National Library of Medicine's Clinical Trials Registry on the world wide web at http://www.clinicaltrials.gov.

In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication in an open access journal and/or posted in a publicly accessible database of clinical trial results.

However, the PI undertakes not to make any publication or release pertaining to the study and/or results of the study without the sponsor's prior written consent, being understood that the sponsor will not unreasonably withhold its approval.

The investigator shall not use the name(s) of the sponsor and/or of its employees in advertising or promotional material or publication without the prior written consent of the sponsor. The sponsor shall not use the name(s) of the investigator and/or the collaborators in

advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The sponsor has the right to publish the results of the study at any time provided the PI has provided input into the manuscript within a 30-day time frame from request.

14.8. Discontinuation of the Study

The sponsor, PI, HREC/IRB and Regulatory Authorities independently reserve the right to discontinue the study at any time for safety or other reasons. This will be done in consultation with the sponsor where practical. In the event of premature trial termination or suspension, the above-mentioned parties will be notified in writing by the terminator/suspender stating the reasons for early termination or suspension (with the exception of the sponsor's responsibility for notifying the Regulatory Authorities). After such a decision, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the participants' interest and safety. All ongoing participants will be followed up for a minimum of 65-75 days after administration of tafenoquine and will be scheduled for an early discontinuation visit or EOS evaluation visit (whichever is applicable). At this visit all assessments scheduled for the EOS evaluations (Week 64) will be performed as described in section 8.4.

14.9. Study Audit

Audits may be carried out by sponsor quality assurance representatives, local authorities or authorities to whom information on this study has been submitted. All documents pertinent to this study must be made available for such inspections after adequate notice of intention to audit.

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APPENDIX 1. SD-OCT FINDING

OCT CST – automated segmentation performed by the Heidelberg Spectralis OCT device will generate an average thickness of the retina in the central 1 mm zone, measured from top of the Internal Limiting Membrane (ILM) to bottom of the RPE (in µm).
OCT TMV – automated segmentation performed by the Heidelberg Spectralis OCT device will generate an average thickness of the retina in the central 6 mm zone, from the top of ILM to the bottom of RPE which provides a volume measurement of the central 6 mm zone (in cubic millimeters).
OCT Parafoveal (inner ring) and perifoveal (outer ring) Retinal Thickness – automated segmentation performed by the Heidelberg Spectralis OCT device will generate an average thickness of the retina in a rim region between the central 1 mm and 3 mm diameter rings and 3 and 6 mm diameter rings, measured from top of the ILM to bottom of the RPE (in µm).
OCT Subretinal Fluid Thickness – manual measure of greatest linear height of any sub retinal fluid (if present) (in µm).
***En face* OCT ellipsoid zone disruption** – manual measurement of the greatest linear extent of ellipsoid layer loss due to foveal photoreceptor damage based on en face OCT scans segmented to the level of ellipsoid zone. Results will be reported as normal or abnormal.
***En face* OCT retinal pigment epithelium layer disruption** – manual measurement of the greatest linear extent of loss of RPE layer due to drug toxicity based on en face OCT scans segmented to the level of RPE layer. Results will be reported as normal or abnormal.
***En face* OCT interdigitation zone disruption** – manual measurement of the greatest linear extent of preserved interdigitating layer due to perifoveal photoreceptor damage based on en face OCT scans segmented to the level of interdigitating layer. Results will be reported as normal or abnormal.

APPENDIX 2. qFAF FINDINGS

Increase in quantitative auto fluorescence in central macula – The Delori grid is placed on the qFAF image with its edge just touching the optic nerve head. There are 29 zones within the grid and average qFAF units in the 4 rings are calculated after blood vessels are masked. A 12% increase in qFAF units in the mid ring (8 zones) would exceed test-retest variability and will be considered a change from baseline.
Area of abnormal auto fluorescence– quantitative assessment of any abnormal patterns of auto fluorescence in the macular region that may be indicative of disease of the RPE (Donnalpally 2017). The pattern of auto-fluorescence will be reported as normal or abnormal.
Decrease in auto fluorescence in central macula – qualitative assessment of decreased intensity of auto fluorescence noted within the central 6000 µm diameter is indicative of decreased function of RPE, masking or even RPE atrophy. This will be reported as Yes/No to presence of hyper-auto fluorescence or hypo-auto fluorescence.
Geographic atrophy of the RPE – quantitative measure of areas of missing RPE; no production of auto fluorescence (area of the region of hypo-auto fluorescence), representing region of RPE death (in square millimeters).

APPENDIX 3. ESTIMATE OF TOTAL BLOOD VOLUME COLLECTED DURING THE STUDY PERIOD

Note:

Total blood sampling volume for the individual participants participating in the study is approximately 135 mL.

The actual times of blood sampling may change. Additional blood samples may be taken for safety assessments as required by the PI or at times specified by the sponsor, provided the total volume taken during the study does not exceed 140 mL during the study including planned blood draws.

Procedure	**Sample**	**Volume per sample (mL)**	**No. samples per participant**	**Total volume per participant (mL)**
Laboratory test	G6PD testing	Blood volume for this sample will come from 4 mL hematology tube at screening		
	CBC	4	8	32
	MetHb%	4	7	28
	Biochemistry	5	7	35
	Serology	5	1	5
	Endocrinology (pregnancy)	5	2	10
Pharmacokinetic test	PK analysis	5	5	25
			TOTAL	**135**

APPENDIX 4. CENTRAL FOVEAL THICKNESS (CENTRAL 1 MM CIRCLE) ON SPECTRALIS DEVICE

Normative interval based on a literature review of the following publications:

Mean = 260 to 280 µm: take 270 µm (across different races)

SD ranges from 16 to 24: take 24 µm (the largest study has this SD)

Mean ± 2 SD = 222 to 318 µm (cover male and female range) using 24 µm as the SD

Citation	CFT Finding
Grover 2009	20-40 years old: 275 ± 24 (N = 19) 41-60 years old: 269 ± 22 (N = 20) 61+ years old: 263 ± 20 (N = 11)
Wenner 2011	N = 34 adults aged 19-30 years old. 29 scan pattern: 281 ± 17 49 scan pattern: 281 ± 17 97 scan pattern: 281 ± 17
Choovuthayakorn 2012	N = 368 adults aged 49 ± 17 years old. Whole group: 259 ± 19 Male: 265 ± 19 Female: 252 ± 18
Appukuttan 2014	N = 105 adults aged 20-75 years' old Whole group: 260 ± 19 Male: 266 ± 19 Female: 255 ± 16

APPENDIX 5. LEEDS SLEEP EVALUATION QUESTIONNAIRE

How would you describe the way you currently fall asleep in comparison to usual?

1.	More difficult than usual	_____	Easier than usual
2.	Slower than usual	_____	More quickly than usual
3.	I feel less sleepy than usual	_____	More sleepy than usual

How would you describe the quality of your sleep compared to normal sleep?

4.	More restless than usual	_____	Calmer than usual
5.	With more wakeful periods than usual	_____	With less wakeful periods than usual

How would you describe your awakening in comparison to usual?

6.	More difficult than usual	_____	Easier than usual
7.	Requires a period of time longer than usual	_____	Shorter than usual

How do you feel when you wake up?

8.	Tired	_____	Alert

How do you feel now?

9.	Tired	_____	Alert

How would you describe your balance and co-ordination upon awakening?

10.	More disrupted than usual	_____	Less disrupted than usual

APPENDIX 6. DIZZINESS HANDICAP INVENTORY

P1. Does looking up increase your problem?	o Yes o Sometimes o No
E2. Because of your problem, do you feel frustrated?	o Yes o Sometimes o No
F3. Because of your problem, do you restrict your travel for business or recreation?	o Yes o Sometimes o No
P4. Does walking down the aisle of a supermarket increase your problems?	o Yes o Sometimes o No
F5. Because of your problem, do you have difficulty getting into or out of bed?	o Yes o Sometimes o No
F6. Does your problem significantly restrict your participation in social activities, such as going out to dinner, going to the movies, dancing, or going to parties?	o Yes o Sometimes o No
F7. Because of your problem, do you have difficulty reading?	o Yes o Sometimes o No
P8. Does performing more ambitious activities such as sports, dancing, household chores (sweeping or putting dishes away) increase your problems?	o Yes o Sometimes o No
E9. Because of your problem, are you afraid to leave your home without having someone accompany you?	o Yes o Sometimes o No
E10. Because of your problem have you been embarrassed in front of others?	o Yes o Sometimes o No
P11. Do quick movements of your head increase your problem?	o Yes o Sometimes o No
F12. Because of your problem, do you avoid heights?	o Yes o Sometimes o No
P13. Does turning over in bed increase your problem?	o Yes o Sometimes o No
F14. Because of your problem, is it difficult for you to do strenuous homework or yard work?	o Yes o Sometimes o No
E15. Because of your problem, are you afraid people may think you are intoxicated?	o Yes o Sometimes o No
F16. Because of your problem, is it difficult for you to go for a walk by yourself?	o Yes o Sometimes o No
P17. Does walking down a sidewalk increase your problem?	o Yes o Sometimes o No
E18.Because of your problem, is it difficult for you to concentrate	o Yes o Sometimes o No
F19. Because of your problem, is it difficult for you to walk around your house in the dark?	o Yes o Sometimes o No

DIZZINESS HANDICAP INVENTORY (CONT)

E20. Because of your problem, are you afraid to stay home alone?	o Yes o Sometimes o No
E21. Because of your problem, do you feel handicapped?	o Yes o Sometimes o No
E22. Has the problem placed stress on your relationships with members of your family or friends?	o Yes o Sometimes o No
E23. Because of your problem, are you depressed?	o Yes o Sometimes o No
F24. Does your problem interfere with your job or household responsibilities?	o Yes o Sometimes o No
P25. Does bending over increase your problem?	o Yes o Sometimes o No

APPENDIX 7: COLUMBIA-SUICIDE SEVERITY RATING SCALE

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency ____
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration ____
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability ____
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents ____
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation ____
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

C-SSRS—Since Last Visit (Version 1/14/09) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

C-SSRS—Since Last Visit (Version 1/14/09) Page 2 of 2

APPENDIX 8: PROTOCOL AMENDMENTS

Version	Date	Significant Revisions
7.0	21Nov2018	• For clarity, the C-SSRS interview will be conducted every 4 weeks ± 1 week rather than monthly to be consistent with the weekly study schedule. Also the interview can be conducted by phone at all visits or in person, if logistically more practical at clinic visits. The responses can be recorded onto a paper CRF or directly into an eCRF. • The list of acceptable methods of birth control and sterilization procedures have been expanded. Flexibility to the timing of the 1a and 1b visits was added to allow sites to schedule subjects optimally for both to complete all assessments. • Laboratory exclusion criteria were revised for clarity. • Section 2.1. The following sentence was added: Tafenoquine under the tradename of KODATEF™ was approved by the Australian Therapeutic Goods Administration in September 2018. • Section 5.4. The data to be collected for early withdrawal of subjects was clarified with respect to recording dates of withdrawal or lost to follow-up to be recorded on the eCRFs.
6.0	05Aug2018	• The names and locations of the two US sites and site principal investigators were added where appropriate (Cover Page, Synopsis, Section 5.8). • A central IRB, Integreview IRB, will be used for the US sites. IRB relevant language was added to the protocol (Cover Page). • A local medical monitor (LMM), to be named, was added for the US sites (Cover Page). • The name of the bioanalytical laboratory for the US site PK analysis was added (Cover Page). • The mfERG evaluation was removed from the study as secondary ophthalmic evaluation (Synopsis, Section 1, Section 2.1.1.3, Section 3, Section 5.2.2, Section 8.1, Section 8.5, Section 9.2.6, Section 10.11.1, Section 12.2.3.2). • The C-SSRS to be conducted at baseline and monthly through Week 64 was

Version	Date	Significant Revisions
		added as an assessment based on US FDA request (Synopsis, Section 1, Section 3, Section 8.2, Section 8.3). • The proportion of subjects with suicidal ideation or suicide attempt by C-SSRS interview was added as a secondary endpoint (Synopsis, Section 5.2.2, and Section 12.2.3.2) • The male birth control exclusion criteria was removed from the protocol as male birth control for men is not a recommendation in the FDA approved product label for tafenoquine (Synopsis, Section 1, Section 6.1). • The window for the Weeks 12, 24, 52, 64, 76, 89, and 194 visits were changed from ± 1 week to ± 2 weeks (Section 1, Section 8.6). • Section 2.1 and Section 5.3 - Information about the US FDA approvals of tafenoquine for the prophylaxis or malaria and the radical cure treatment of P vivax malaria was added. • Section 3 and Section 5.6 - Visit dates were updated. • Section 5.1 - Clarification of the screening visits activities was provided. • Section 5.5.1.2. - Serious hypersensitivity reactions were added as a possible systemic reaction. • Section 6 - The racial groups (all) included in the study was clarified. Also, the responsible persons for reviewing subject eligibility was revised due to the addition of the US clinical sites. • Section 6.2, exclusion criteria #2, hemolytic anemia was added. • Section 6.2, exclusion criteria #9a, "History of psychotic disorders or current psychotic symptoms (hallucinations, delusions, or grossly disorganized thinking or behavior) was added and #9b "Current (past year) suicide behavior disorder" was also added. • Section 6.3 - Explanation that the first digit of the subject ID number will reflect the site number was added. • Section 7.2.1 - "Temperature excursions are permitted to 15°C to 30°C (59°F to 86°F)" was added to be consistent with the US Prescribing Information.

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		• Section 7.3.1 and 7.3.2 were revised for clarity of the Mosio system. • Section 7.5.1 was revised to clarify the use of the diary cards and the Mosio system for drug compliance. • Section 8.5 was clarified that ophthalmologic assessments to be conducted during the Part 3 follow-up visits (in the event of an ongoing AE) only included those that revealed an abnormality or any additional assessments needed to evaluate the abnormality at the discretion of the investigator. • Section 9.1 was clarified regarding the definition of baseline assessments. • Section 9.2.7 added that psychiatric conditions could be further evaluated by a Study Psychiatrist or Psychologist. • Section 9.2.10 was added to describe the C-SSRS. • Section 10.11.1.1 - Methemoglobin > 10% was added as an AESI. • Section 10.11.4 - Reporting Information of SAEs for US sites was added. • Section 12.2.3 - Shift tables will be presented for selected laboratory tests was added in addition to mean and change from baseline levels. • Section 15 - The Oquendo reference for the C-SSRS assessment was added. • Appendix 4 – Placing a copy of the MINI exam as an appendix was removed. • Appendix 7 - The C-SSRS assessment was added.
5.0	02 Apr 2018	• Section 1.0 – The Study Schedule of Events was revised to allow 6 weeks for screening, a ± 3 days window at Week 4, and a ±1 week window at Week 12. • Section 5.4 (Individual Subject Withdrawal) was clarified to provide more details regarding the assessments to be performed in the event of subject withdrawal. • Section 6.2 Exclusion Criteria were revised as follows: Criterion #10 – A new sentence was added to provide for the use of prescription and non-prescription medications containing codeine. Criterion #15 – Language was added to allow the Investigator to include subjects with out-of-range hematology results that were not judged as clinically significant. Criterion #16 – Language was added to allow the Investigator to include subjects

Version	Date	Significant Revisions
		with out-of-range biochemistry results that were not judged as clinically significant. • Section 8.6 (Assessment and Visit Windows) – The Visit Windows were updated to be consistent with the revised Study Schedule.
4.0	07 Feb 2018	• Due to slow recruitment of subjects at Linear Clinical Research, it was decided to expand this study to a multisite study and clinical sites in the United States. • Randomizations will use clinical site as a stratification variable as the study was changed to a multisite study. • Exclusion criteria #3(l) was revised to an SD-OCT CSF thickness of <222 µm or >318 µm instead of from <240 µm to >300 µm. This change was also made to Appendix 5. This criteria was established based on the SD of this measurement from several published studies and rather than use the smaller of the two ranges of SD of 16, it was changed to the larger SD of 24 to set the range at a well established 95% confidence interval for the normal range of thickness in the literature for normative values. • Normal medical urinalysis was removed as an inclusion criterion as other biochemistry parameters were considered more indicative of a clinically significant medical condition. • Hematology and biochemistry inclusion parameters were deleted and instead, specific ranges for hematology and biochemistry laboratory values were added as two new exclusion criteria (criteria 15 and 16). • Clarification of the psychiatric exclusion criterion was added. • Updated section 7.2.1 to reflect the investigational product storage temperature on the drug label to 15°C to 25°C.
3.0	20 Sep 2017	• Adjusted protocol to reflect FDA advice “FDA comments on the May 31st, 2017, submission to IND 129656”. • The proposed primary endpoint evaluation criteria shown in Table 4 was considered too strict by the Agency, leading to the possibility of a large number of participants being assessed as having a significant retinal change from baseline. The

Version	Date	Significant Revisions
		Agency recommended that the OCT CST be revised to define a change from baseline of at least 40 µm as clinically significant. The Agency also recommended that OCT TMV be revised to define a change from baseline of 10% or more as clinically significant. • The Agency requested the actual SD-OCT image of the ach eye be included in the eCRF. • The Agency requested that the analysis of BCVA is based on a one line, 2 line or 3 or great line change in BCVA from baseline. A three-line change in ETDRS BCVA at 4 m should be considered clinically significant. This adjustment was made but included letter changes to avoid rounding errors. • The Agency suggested FM-100 colour vision test (gold standard) is used in preference to the Farnsworth-Munsell (FM) 15 hue test. This should be a binocular test with the Lanthony D15 test administered prior to disrupt learning effects. • The Agency requested that the grading of corneal deposits does not use the LOCS III transparency grading scale (Chylack 1993). This scale has previous been adjusted in version 2.0, dated 19 July 2017. • The Agency requested copies of the CRF, OCT protocol handbook, and FAF protocol handbook be submitted for review. • ECG at baseline and at least one follow-up time point was requested during the treatment period. • The Agency requested monitoring of all patients in the study for safety out to 10 to 12 weeks (Week 62 to 64) after the last dose of tafenoquine because of its long washout period (65-75 days). The participants who experience an AE would then continue in the follow-up phase as per the protocol. • The protocol should specify the assay(s) used to measure methemoglobin. • The Agency requested that participants who are withdrawn from the study before Week 12 are not replaced and that all randomized participants, including participants who discontinue treatment early, continue to be followed through study completion. Reasons for study discontinuation should be documented on the eCRF and the protocol should provide details for how participants who withdraw from the study

Version	Date	Significant Revisions
		prematurely or discontinue treatment will be handled in the statistical analyses. • The Agency recommended sample size calculations and primary analysis be based on an alpha level of 5% two-sided. • The Agency recommended that participants are analyzed as they are randomized in the study. • The Agency recommended that the definitions of the primary endpoint listed in Section 5.2.1 and 12.2.3.1 of the protocol is modified to remove reference to the TQ group, as the primary endpoint should be applicable to both treatment arms in the study. • Section 9.2.6 Clarified that the trained sub-investigators will be performing the M.I.N.I. and not specifically trained psychiatric nurses. • Adjusted wording so subject is substituted for participant. • Adjusted descriptions of corneal and retinal photography to include both conventional and wide field imaging (to capture 200° of internal angle of the retina). • OCT will include wide field macular scan. • qFAF will be a set of 3 images to ensure consistency in measurements. • Updated Section 5.1 and 5.6. Recommended volume of water to take tablets is 180 mL not 240 mL. Aligns to FDA advice provided for Study TQ-2016-01 (PK study). • Updated Section 6, 7.7, 8.1 and 10.5 to clarify that the sub-investigator is responsible for non-ophthalmic and ophthalmic eligibility assessments at Linea Clinical Research and the Lion's Eye Institute respectively. The sub-investigator will confirm eligibility with the PI as appropriate. The PI may further confirm eligibility with the LMM. • Updated Section 6.2. SD-OCT thickness for exclusion criteria is now aligned with Appendix 5 (230-310 µm) which is the mean $\pm$ 2 standard deviations. • Section 8.2. Clarified dosing starts on Day 1, Week 1 (3 day loading dose of 2 x 100 mg tablets for 3 days, followed by weekly dosing (2 x 100 mg tablets) on the same day as Day 3, starting 7 days later.

Version	Date	Significant Revisions
		• Section 8.2. Removed 60 minute window after procedures for releasing from clinic. At the judgment of the investigator • Section 8.3. Removed "Week 1, Day 1" as this Visit 2 is covered in Section 8.2 and was confusing. • Section 8.6. Removed pre-dose observations within 60 minutes prior to dosing and other specific interval discussions. Week windows are adequate. • Section 9.2.6. Clarified that a study nurse or research physician who is trained in the M.I.N.I. 7.0.2 may administer the test. This was later clarified in version 3.0 to only allow sub-investigators trained on the M.I.N.I. by Dr. Sheehan (inventor).
2.0	19 Jul 2017	• Updated Table 1 text to reflect separation of Screening and EOS over 2 consecutive days, separating EOS into Visits 7a and 7b. Also to outlined the order of eye assessments to be clearer and added biometry assessments and MARS contrast sensitivity test. • Adjusted primary endpoint measure wording. • Adjusted "proportion of participants who develop a loss of 0.12 or greater logarithm of contrast sensitivity (LogCS) on the MARS contrast sensitivity test. • Adjusted SD-OCT parameters to examine the ellipsoid and interdigitating zone integrity and continuity. • TMV and parafoveal inner ring of ETDRS grid thickness will also be examined. • Retinal digital photography to be conventional and wide field to enable detection of subtle peripheral toxicity. • Table 4: Included quantitative assessment of both central subfield and inner zone of the ellipsoid zone for SD-OCT • Table 4: Included grading of ellipsoid zone as present (complete), patchy (some disruption), or absent. • Table 4: Clarified Lions Eye Institute would be responsible for the primary read • Included interdigitating zone integrity testing • Updated Section 2.3.2 with Table 3 Adverse Events occurring in ≥1% of Participants in the Tafenoquine ACR Group and with an Incidence Numerically

Version	Date	Significant Revisions
		Greater than in the Placebo Group • Updated Section 6.2. Updated Exclusion criteria 9 to manage subjects who have a positive finding on M.I.N.I at Screening for follow-up referral to their GP after Study Psychiatrist diagnosis. • Minor adjustments to other exclusion criteria. • Section 6.4.2 removed references to phenformin, butformin and pilsicamide which are not available in Australia. • Updated Section 7.2.4. Included handling of new or worsening psychiatric AE by M.I.N.I to reflect HREC/HRPO questions • Section 7.3. Updated with information about the Medication Adherence and Reminder System (Mosio) (Section 7.3.1, 7.3.2 and 7.3.3) • Updated Section 7.5.1 with compliance mechanism using Mosio • Updated Section 7.7. Participants are not to be told about corneal deposits. • Adjusted Section 8.1. Clearer sequence of ophthalmic testing. • Updated Section 8.3. Clearer sequence of ophthalmic testing. Included Orlando grading system for corneal deposits and not the cataract grading system (Chylack). Clarified abnormal follow-up would include the MARS contrast sensitivity test. Slit lamp examination and digital photograph of corneal surface will examine cornea Verticillata and retinal digital photography will examine toxic maculopathy and retinopathy on conventional and wide field images. • Updated Section 8.4. Full field ERG incorporating ISCEV standards, MARS letter contrast sensitivity and M-Chart will be used to follow-up abnormal findings. Corneal deposits and retinal lesions from drug toxicity at Week 52 need to be monitored by slit lamp examinations, SD-OCT, qFAF and photography. • Updated Section 8.5. EOS ophthalmic visits scheduled over two days. Clarified sequence of ophthalmic testing. • Updated Section 9.2.5. Clarified ophthalmic testing sequence. Results from blinded fundus reading center will be reviewed by PI. • Updated Section 9.2.6. Handling of new or worsening psychiatric AE by M.I.N.I

Version	Date	Significant Revisions
		to reflect HREC/HRPO questions. • Section 10.11.1. Clarified significant deterioration in the MARS contrast sensitivity test in an AESI. • Section 12.2.3.1. Clinically significant changes for quantitative measures will include a threshold taken from previously published coefficients of repeatability. If automated reading is missing or unreliable, the parafoveal (inner ring of the ETDRS grid), the annular zone between foveal center (1 mm diameter circle and 3 mm diameter circle) and retinal thickness will be used to impute missing data. • Table 5 updated. • Section 12.3.3.2 updated. Includes proportion of participants who develop a loss of 0.12 or greater log CS on the MARS contrast sensitivity test. • En face reflectivity profile of the ellipsoid and interdigitating zone (integrity and continuity). Orland 1984 grading system for cornea Verticillata grading used to replace “cataract” system of Chylack 1993 • Updated Section 14.2.1. All non-substantial changes will be notified to the HREC/HRPO • Updated Section 15.0. Included reference for M.I.N.I version 7.0.2 (Sheehan 1998). Deleted Chylack 1993. Added Orlando 1984 and Donnalpally 2017. • Appendix 1: Updated to state “qualitative assessment of disruption of ellipsoid layer in the central subfield and inner zone indicative of photoreceptor dysfunction.” • Updated with OCT parafoveal assessments (inner ring of EDTRS grid) • En face OCT ellipsoid zone disruption • En face OCT retinal pigment epithelium layer disruption • En face OCT ellipsoid zone preservation • En face OCT interdigitating zone preservation • Appendix 2: Updated to Area of abnormal auto fluorescence – quantitative assessment of any abnormal areas of auto fluorescence in the macular region that may be indicative of disease of the RPE. • Added/adjusted. Areas of abnormal auto fluorescence, decrease in auto

Version	Date	Significant Revisions
		fluorescence in the central macula and geographic atrophy of the RPE. • Appendix 2: Cited Donnalpally 2017 • Appendix 5. Clarified units of measurement