60º Pharmaceuticals LLC

Clinical Protocol
NCT04533347

Protocol Title:	A double-blind placebo-controlled study to assess the efficacy and safety of oral tafenoquine versus placebo in patients with mild to moderate COVID-19 disease
Protocol Number: IND	TQ 2020_06
Number: Sponsor	152009
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Signature Page

Protocol Number: TQ 2020_06

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The signatures below indicate approval of the protocol.

Sponsor Representative: _____ _____

Geoffrey Dow — Date

CEO

Investigator's Statement of Agreement:

I acknowledge possession of and have read the tafenoquine Investigator's Brochure and this protocol. Having fully reviewed all the information provided, I consider it ethically justifiable to give the study drug to patients according to the agreed protocol. I will conduct the study in full accordance with this protocol and all applicable laws and regulations, including but not limited to current Good Clinical Practices.

Investigator: _____ _____

(Signature) Date

_____

(Printed Name)

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
ACE2	angiotensin-converting enzyme II
AE	adverse event
ALT	alanine transaminase
ARDS	Acute Respiratory Distress Syndrome
AST	aspartate aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
BUN	blood urea nitrogen
CDMS	clinical data management system
CFR	Code of Federal Regulations
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CRF	case report form
CYP	cytochrome P450
DMC	Data Monitoring Committee
eCRF	electronic case report form
ePRO	electronic patient-reported outcome
FDA	U.S. Food and Drug Administration
G6PD	glucose-6-phosphate-dehydrogenase
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hERG	human Ether-à-go-go-Related Gene
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IIV	Inter-Individual Variability
INR	international normalized ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MAPK	mitogen-activated protein kinase

Abbreviation/Term	Definition
MATE-1	multidrug and toxin extrusion 1 transporter
MATE2-K	multidrug and toxin extrusion 2K transporter
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N	sample size
N/A	not applicable
NP	Nasopharyngeal
OAT1	organic anion transporter 1
OAT3	organic anion transporter 3
OATP1B1	organic anion transporting polypeptide 1B1
OATP1B3	organic anion transporting polypeptide 1B3
OCT2	human organic cation transporter 2
P-gp	P-glycoprotein
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
PXR	pregnane-X-receptor
RBCs	red blood cells
RR	respiratory rate
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-Cov-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SOPs	standard operating procedures
T_{max}	time to maximum concentration
TQ	Tafenoquine
WBC	white blood cell

2 PROTOCOL SYNOPSIS

Protocol Title:	A double-blind placebo-controlled study to assess the efficacy and safety of oral tafenoquine versus placebo in patients with mild to moderate COVID-19 disease
Protocol Number:	TQ 2020_06
Sponsor:	60º Pharmaceuticals LLC
CRO:	Peachtree Bioresearch Solutions, Inc.
Study Sites:	Multiple sites in USA or elsewhere as appropriate. Sites must have: • Capacity to conduct Food and Drug Administration (FDA)-authorized real-time polymerase chain reaction (RT-PCR) SARS-CoV-2 test and provide results within 48 hours • Access to point of care glucose-6-phosphate-dehydrogenase (G6PD) testing or be able to receive G6PD test result from an in-house or commercial laboratory within 48 hours • Pharmacy with capability to dispense study medication in secondary child-proof containers with appropriate labelling
Study Phase:	Phase 2
Study Objectives:	Primary Objective: The primary objective is to determine if tafenoquine (TQ) [trade names ARAKODA™ and KODATEF™] increases the proportion of patients with clinical recovery from COVID-19 symptoms on Day 12 in patients with mild to moderate COVID-19 disease compared with placebo. Clinical recovery on Day 12 is defined as: • Temperature - ≤37.7°C [oral or skin surface] • Respiratory rate ≤ 24/minute on room air • Shortness of breath - absent • Cough – mild or absent on a patient reported scale of absent, mild, moderate, and severe Secondary objectives include determining if TQ: • Increases the proportion of patients with absence of detectable SARS-CoV-2 virus by RT-PCR at Day 12 • Increases the proportion of patients with absence of clinical symptoms by individual symptom at Day 12 • Decreases the hospitalization rate due to COVID-19 disease by Day 12 • Decreases the number of medical follow-up visits by Day 12
Study Design	This study is a double-blind, randomized, multisite, placebo-controlled trial comparing the safety and efficacy of TQ with placebo in non-hospitalized patients with mild to moderate COVID-19 disease. Patients will undergo screening procedures from Day -4 to Day -1 including G6PD testing, an FDA-authorized RT-PCR test (from nasopharyngeal [NP] swab specimens) to confirm presence or absence of SARS-CoV-2, pregnancy testing, hematology, blood chemistry, vital signs, O_2 saturation, physical exam, and assessment for symptoms of COVID-19 disease including cough, shortness of breath, respiration rate, and temperature. On Day 1, eligible patients will either return to the clinic or may have a telemedicine visit. Continued eligibility will be reviewed, and if still eligible, patients will be randomized and will receive and self-administer 200 mg TQ or matching placebo on Days 1, 2, 3, and 10

	[each administration of drug will be within ± 1 day with the exception of the first dose]. If the Day 1 visit is a telemedicine visit, the randomized blinded study drug will be sent via courier to the patient. Patients will be provided an oral thermometer to check and record their daily temperature and a home pulse oximeter to record their daily oxygen saturation. Patients will also be provided with an electronic study diary (eDiary) (loaded onto a device of their choosing) and be required to complete the eDiary entries from Day 1 through Day 12 [± 1 day]. Patients will record respiration rate, temperature, COVID-19 clinical signs including presence and severity of cough, respiration rate and shortness of breath, AEs, and concomitant medications in the electronic diary daily. They will also record study drug administrations in the diary to monitor compliance. Daily diary data will be automatically uploaded to the electronic data management system and will be reviewed daily by clinical staff. Patients will be contacted by telephone or videoconferencing by designated study personnel on a daily basis to review AEs for severity by asking an open ended question, check for use of concomitant medications, and if there are new or worsening signs and symptoms of COVID-19 disease from Day 1 through Day 11 [± 1 day]. Telemedicine interviews will follow a script and information will be recorded in source documents. If a suspected SAE or worsening of signs and symptoms of COVID-19 are reported, a study physician will be contacted to determine if the patient needs additional support (clinic visit, medication, or emergency room visit). If the patient cannot be reached, an individual from their emergency contact list will be contacted to determine if the patient has been hospitalized. Patients will return to clinic on Day 12 [± 1 day] for the assessments listed in Table 1. From Day 13 [± 1 day] through Day 28 [± 1 day], patients will be instructed to complete the eDiary and will have a final telemedicine call on Day 28 [± 1 day].
Primary Efficacy Endpoint:	• Proportion of patients with clinical recovery of COVID-19 symptoms on Day 12 [± 1 day]
Secondary Efficacy Endpoints:	• Proportion of patients with negative SARS-CoV-2 RT-PCR on Day 12 [± 1 day] • Hospitalization rates due to COVID-19 symptoms (excluding admittance only for administrative or observations purposes) • Number of COVID-19-related medical follow up visits [Doctor's office or emergency room (ER) visit] • Proportion of patients with COVID-19 symptoms at Day 12 by individual symptoms
Exploratory Efficacy Endpoints:	• Time to maximum severity of COVID-19 symptoms after start of treatment • Time to resolution of COVID-19 symptoms including cough, fever, shortness of breath and elevated respiratory rate. • Proportion of patients clinically recovered at Day 28 [± 1 day]
Safety Endpoints	• Adverse events (AEs) and serious adverse events (SAEs) • Vital signs (respiratory rate, temperature, heart rate, blood pressure, O_2 saturation) • New symptoms of COVID-19 disease not present at screening • Clinical chemistry and hematology
Study Drug and Administration:	TQ will be administered orally as 2 x 100 mg dark pink coated tablets [or matching placebo] on Days 1, 2, 3, and 10. Placebo will be a identically appearing tablet containing excipients.
Planned Participants:	Approximately 275 patients with mild to moderate infection with COVID-19 will be enrolled with the goal of reaching 250 patients meeting the criteria for the modified intention-to-treat (mITT) population.

Participant Selection:	**Inclusion criteria:** (1) Male or female, aged ≥18 years of age; (2) Laboratory confirmed infection with COVID-19 virus by an FDA-authorized SARS-Cov-2 RT-PCR; (3) Able and willing to give written informed consent. (4) Willing to keep an electronic diary from Study Day 1 to Day 12 [± 1 day] and have daily phone or videoconferences with study team personnel. (5) At least one of the following clinical symptoms of COVID-19 infection within the 4 days prior to and inclusive of the day of screening: a. Respiratory rate ≥ 24/min: b. New cough or shortness of breath that has presented within the last 4 days; c. Fever – temperature ≥ 37.7°C [oral or skin surface] (6) Must agree not to enroll in another study of an investigational agent prior to completion of Day 28 of the study. (7) Able to take ARAKODA or KODATEF according to Prescribing Information (8) Have been symptomatic no longer than 5 days when the first dose of study medication is administered. (9) If female, agree to use an acceptable method of birth control from the time of consent through 56 days after the last dose of study drug. **Exclusion criteria:** (1) Have of the contraindications for ARAKODA or KODATEF in the prescribing information (Section 15.1) including: a. G6PD deficiency b. Breastfeeding c. Psychotic disorder or current psychotic symptoms d. Known hypersensitivity reaction to TQ (2) Evidence of severe or critical illness, defined by at least one of the following: a. Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥30 breaths per minute, heart rate ≥ 125 beats per minute, SpO2 ≤93% on room air b. Respiratory failure defined based on resource utilization requiring at least one of the following: i. Endotracheal intubation and mechanical ventilation, oxygen delivered by high flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, extracorporeal membrane oxygenation (ECMO), or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation) ii. Shock (defined by systolic blood pressure < 90 mmHg, or diastolic blood pressure <60 mmHg or requiring vasopressors) iii. Multi-organ dysfunction/failure (3) Any other clinically significant acute illness unrelated to COVID-19 within seven days prior to first study drug administration

	(4) Receipt of any experimental treatment for COVID-19 (off-label, compassionate use, or study-related) within the 30 days prior to the time of the screening evaluation (5) Any excluded concomitant medication as described in the ARAKODA package insert [Section 15.1] (6) Any COVID-19 symptoms which, in the opinion of the investigator, is suggestive of possible requirement to hospitalize within 48 hours of enrollment (7) Positive pregnancy test (8) Have been symptomatic for more than five days when the first dose would be administered
Treatment Groups:	There will be 2 treatment groups; TQ and placebo for which at least 250 patients will be randomized in 1:1 ratio to treatment with clinical site as a stratification variable. Randomizations will continue until at least 250 patients meet the criteria for mITT.
Screening Procedures:	After signing informed consent, patients will be screened for eligibility including medical history, G6PD, RT-PCR for SARS-CoV-2, pregnancy testing for females of child-bearing potential, hematology, blood chemistry, vital signs, O_2 saturation, and physical exams. The Screening period will be a maximum of 4 days (Days -4 to -1), and the first day of dosing will be Study Day 1.
Randomization Procedure:	Eligible patients will be randomized at a 1:1 ratio to receive TQ or placebo. Randomization will be performed through a centralized, web-based, validated system that automates the assignment of patients to treatment allocation. Randomization will be stratified by clinical site.
Efficacy Assessments:	• Clinical signs and symptoms of COVID-19 (clinically diagnosed and patient reported) including fever, shortness of breath, cough, and respiratory rate daily from Day 1 to Day 28 (Note, the clinical signs of COVID-19 will not be reported as AEs) • SARS-CoV-2 PCR at Day 12 ± 1 day. • Hospitalization
Safety and Tolerability Assessments:	**Clinical:** • Vital signs (blood pressure, heart rate, and O_2 saturation) • AEs **Laboratory:** • Hematology: red blood cells (RBC), white blood cells (WBC) with partial differential (neutrophils), hematocrit, hemoglobin, platelets; C-reactive protein (CRP), international normalized ratio (INR), prothrombin time (PT)/ partial thromboplastin time (PTT) • Blood chemistry: blood urea nitrogen (BUN), creatinine, alanine transaminase (ALT), and aspartate aminotransferase (AST) • Pregnancy test
Statistical Analysis:	<u>Analysis Populations:</u> • The modified Intention-to-Treat (mITT) population will include all patients who took at least one dose of study medication and had at least one post baseline assessment. The mITT population will be analyzed as they are randomized, regardless of which treatment a patient received. • Safety population: Any patient randomized and received any dose of study drug. Safety population will be analyzed based on the actual treatment received. • The PP population includes all mITT patients who completed the Day 12 clinic visit without any major protocol deviations. Protocol deviation category (minor or major) will be determined prior to the database lock and unblinding.

	Primary Efficacy Endpoint: The proportion of patients with clinical recovery at Day 12 will analyzed using two methods: a 2x2 contingency table and logistic regression. The contingency table will provide unadjusted estimates of the proportions of patients with clinical recovery at Day 12. Copper-Pearson exact 95% confidence intervals around the recovery proportion within each treatment group will be provided. In a logistic regression treatment group will be the primary independent factor, additional covariates will be included in the model if there are sufficient events. Patients who do not have a Day 12 visit due to hospitalization for COVID-19 symptoms will be considered treatment failures Other Efficacy Endpoints: Dichotomous secondary endpoints will be analyzed in the same manner as the primary endpoint. The number of medical follow-up visits tabulated to determine if the endpoint can be considered continuous or ordinal. If the data are continuous the treatment groups will be compared by t-test. If the frequency distribution indicates few numbers of visits (e.g., 0, 1, 2, and 3 visits) then the analysis will use a chi-squared test to compare treatment groups. Safety Endpoints: AEs will be coded using the most recent version of the Medical Dictionary of Regulatory Activities (MedDRA) preferred terms and will be grouped by system, organ, and class (SOC) designation. The incidence of new COVID-19 symptoms not present at screening will be reported separately from other AEs including the maximum severity and time of maximum severity relative to the start of investigational product. The severity, frequency, and relationship of AEs to investigational product will be presented by preferred term by SOC grouping. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided. Each AE (based on preferred terminology) will be counted once only for a given patient. If the same AE occurred on multiple occasions, the highest severity and relationship to investigational product will be assumed. Thus, study participants are not counted multiple times in a given numerator in the calculation of frequencies for a specific AE. Laboratory data and vital signs will be reported as summary statistics and change from baseline by treatment group for the safety population. Justification of Sample Size: Assuming an 85% clinical recovery rate in the TQ group and a 70% clinical recovery rate in the placebo group, sample sizes of 125 per treatment group will achieve 80% power with a two-sided alpha of 0.05 by logistic regression analysis.
Study Duration:	Patients will participate for up to 33 days including up to 4 days for screening, a treatment period over 10 days with safety/efficacy follow-ups through Day 28 [± 1 day].

3 INTRODUCTION

3.1 COVID-19

COVID-19 is an infectious disease caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). It was first identified in 2019 in Wuhan, China, and quickly spread to over 215 countries and territories (Worldometer 2020). As of 03 July 2020, there were more than 2,730,000 cases in the USA with more than 128,000 deaths related to the disease (CDC 2020). Worldwide, as of 03 July 2020, there were more than 11,190,000 cases and 529,000 deaths (Worldometer 2020).

SARS-CoV-2 infects lung alveolar epithelial cells using receptor-mediated endocytosis via the angiotensin-converting enzyme II (ACE2) receptor. ACE2 is expressed on Type I and type II alveolar epithelial cells (Jia 2005). The binding of SARS-CoV-2 on ACE2 causes damage to alveolar epithelial cells that results a series of inflammatory processes (Zhou 2020).

The current pandemic of COVID-19 is associated pulmonary inflammation and Acute Respiratory Distress Syndrome (ARDS) (Zhou 2020). In symptomatic patients, the clinical manifestations of the disease usually start within a week of exposure, and include fever, cough, shortness of breath, nasal congestion, fatigue, and upper respiratory tract infections. Gastrointestinal symptoms and asymptomatic infections have also been reported (Xiao 2020). The infection can progress to severe disease with dyspnea and severe pneumonia in the second or third week of infection, as evidenced by decreased oxygen saturation, blood gas deviations, and chest X ray (or other imaging) changes indicating deterioration. Lymphopenia may be present, and inflammatory markers (C-reactive protein and proinflammatory cytokines) are elevated (Velavan 2020).

Drugs administered late in the course of the disease, when patients are hospitalized with moderate to severe disease, may have minimal benefit (Beigel 2020, Geleris 2020, Wang 2020). It has been proposed that the anti-viral activity of antimalarial drugs may have potential in the treatment of earlier stage disease when symptoms start to emerge by blocking the viral replication cycle. Hydroxychloroquine was tested in nonhospitalized adults with early symptoms of COVID-19 disease and was found to have modest activity in reducing symptoms of infection and well as subsequent hospitalizations compared with placebo, but these differences were not statistically significant (Skipper 2020). TQ was compared with hydroxychloroquine for inhibition of SARS-CoV-2 viral replication and was found to be 4-fold more potent (see Section 3.4). Therefore, TQ is of interest for investigation in early stage disease.

3.2 Tafenoquine (TQ)

Tafenoquine [2, 6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy) primaquine, succinate] is an 8-aminoquinoline, formulated as an oral tablet (100 mg). TQ is a primaquine derivative (Figure 1) with a long half-life of approximately 14 days (Brueckner 1998). As such, TQ is safe and effective (as a prophylactic drug for the prevention of plasmodial infections) with weekly administration.

Figure 1 Structure of Tafenoquine

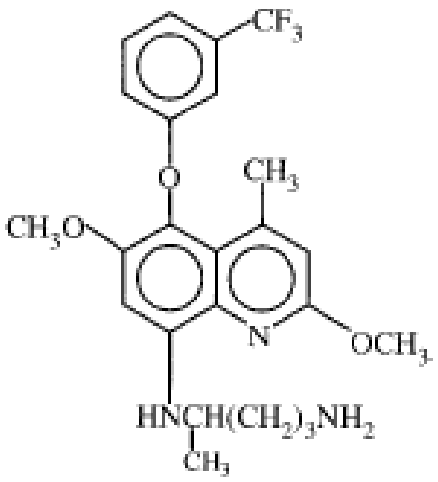


Figure taken from Brueckner 1998.

3.3 Summary of Nonclinical and Clinical Studies

3.3.1 Nonclinical Studies

The key target tissue effects in repeat-dose general toxicology studies of TQ 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 pneumonocytes, and eosinophilic material in alveoli), which were manifested principally in the lung. 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. No ophthalmological changes have been observed in any of the nonclinical animal toxicity studies.

Based on the phospholipidosis-related changes in the lungs, the approximate overall no observed effect dose was 0.5 mg/kg/day (26 weeks) in rats and 0.1 mg/kg/day (52 weeks) in dogs. In separate eight week toxicokinetic studies using the same doses as the repeat dose studies, the no observed effect dose was shown to be associated with plasma area under the curve from Week 0 to Week 1 (AUC_{0-1}) week values of 6.66 µg·h/mL in rats and 6.84 µg·h/mL in dogs (sexes combined). When compared to the AUC in humans consequent to the anticipated clinical regimen of TQ (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 TQ.

In an in vitro human Ether-à-go-go-Related Gene (hERG) channel electrophysiology assay, the inhibitory concentration at 50% (IC_{50}) value for inhibition of hERG tail current was determined to be 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 electrocardiographic evaluations (including QTc interval) conducted in the in vivo oral and intravenous 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 TQ 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, TQ has a low potential for QTc prolongation.

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 reproductive toxicology studies.

Standard mutagenic tests for TQ led to the conclusion that TQ itself does not present a genotoxic risk to man. Refer to the Investigator's Brochure for additional information.

3.3.2 Clinical Studies

Tafenoquine has been approved by the FDA for prophylaxis of malaria in adults (Arakoda™, 60º Degrees Pharmaceuticals, 100 mg tablets) and for radical cure of *Plasmodium vivax* in persons greater than 16 years old (Krintafel™, GSK, 150 mg tablets). The Australian Therapeutics Good Administration has also approved tefenoquine under the trade name of Kodatef™, 60º Degrees Pharmaceuticals, 100 mg tablets).

3.3.2.1 Pharmacology

Despite TQ inhibiting a variety of cytochrome P450 (CYP) enzymes in vitro (including CYP1A2, 2C9, 2D6 and 3A4/5), subsequent clinical studies have shown a low risk of clinically relevant drug-drug interactions via these enzymes. No clinically significant effects on the pharmacokinetics of substrates of CYP1A2 (caffeine), CYP2D6 (desipramine), CYP2C9 (flurbiprofen), or CYP3A4 (midazolam) were observed following coadministration with TQ in healthy adult patients. Furthermore, TQ did not activate the human pregnane-X-receptor (PXR), using an in vitro reporter gene assay, suggesting that TQ is unlikely to perpetrate a drug-drug interaction as a result of induction of CYP3A4.

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 (MATE2-K) with calculated 50% inhibitory concentration (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.

Tafenoquine is not an inhibitor of human breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), Organic anion transporter 1/3 (OAT1 or OAT3), Organic anion transporting polypeptide 1B1/1B3 (OATP1B1 or OATP1B3) mediated transport at clinically relevant concentrations. Tafenoquine is also not a substrate of human OATP1B1 or OATP1B3 at clinically relevant concentrations. It is inconclusive as to whether TQ is a substrate of P-gp and/or BCRP mediated transport.

3.3.2.2 Safety Pharmacology

The effect of TQ on the QT interval was evaluated in a study of healthy adult patients. In this study, patients received once daily 400 mg (2 times the approved recommended dosage) doses of TQ for 3 days. The results suggest that the mean increase in the QTcF interval for TQ is less than 20 msec.

3.3.2.3 Pharmacokinetics

In majority of the clinical studies, TQ was administered under fed conditions. Following single dose administration of 200 mg TQ (two 100-mg TQ tablets) in 65 healthy adult patients under fed conditions (a high-calorie, high-fat meal [approximately 1000 calories with 19% protein, 31% carbohydrate, and 50% fat]), the maximum concentration (C_{max}), time to maximum concentration (T_{max}), and AUC_{inf} were determined to be 147 ng/mL, 14 hr, and 70 hr*µg/mL, respectively. Following administration of a single dose of TQ orally under fasted conditions in healthy adult patients, AUC and C_{max} increased dose proportionally over the dose range from 100 mg to 400 mg. When healthy adult patients received once-weekly administrations of 200 mg TQ orally for ten weeks without a loading dose under fasting conditions, the mean plasma accumulation ratio of TQ was approximately 4.4.

The apparent oral clearance of TQ is approximately 4.2 L/hr (Inter-Individual Variability [IIV]: 23.6 %) in healthy adult patients. The mean terminal half-life following administration of TQ is approximately 16.5 days (range: 10.8 days to 27.3 days) in healthy adult patients. Tafenoquine is greater than 99.5% bound to protein in humans. The apparent volume of distribution of TQ in healthy adult patients is 2470 L (IIV: 24.1%).

3.3.2.4 Efficacy

There have been no clinical studies with TQ in the proposed indication (mild to moderate COVID-19 infection).

3.3.2.5 Safety

The safety of TQ was assessed in clinical studies to support the approval of TQ for prophylaxis of malaria and for radical cure of *Plasmodium vivax* at various doses and regimens in 3,184 patients. The recommended TQ regimen was evaluated in 825 patients in 5 controlled clinical studies. The mean duration of exposure to TQ in these five clinical studies was 21 weeks (range 10-29 weeks). Three studies were conducted in healthy semi-immune (to malaria) volunteers in Ghana or Kenya and were placebo-controlled; a mefloquine arm was included in 2 clinical studies as a benchmark. An additional study, an active comparator (mefloquine) controlled study, was conducted in healthy soldiers deployed in East Timor (Timor Leste), and a placebo-controlled study was conducted in healthy volunteers in the United States and United Kingdom.

Tafenoquine has been generally well-tolerated in clinical studies. The most common adverse events (AEs) include nausea, vomiting, abdominal pain, diarrhea, and reversible vortex keratopathy (whorl-like patterns of corneal epithelial deposits that did not interfere with visual acuity). Gastrointestinal (GI) AEs occurred with a greater incidence in patients treated with TQ compared with placebo and appeared to increase with increasing dose. Methemoglobinemia has been commonly reported following dosing of TQ in all studies and is most likely secondary to TQ-induced oxidative stress within red blood cells (RBCs). Elevations in serum creatinine without changes in glomerular filtration rate have also been observed. Hypersensitivity reactions (urticaria) have been reported in two patients. Hemolytic anemia should be anticipated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency; therefore, patients must undergo G6PD deficiency testing and only be enrolled into TQ studies if G6PD-normal.

Refer to the Investigator's Brochure and/or prescribing information (Section 15.1) for additional information.

3.4 Rationale for the Study

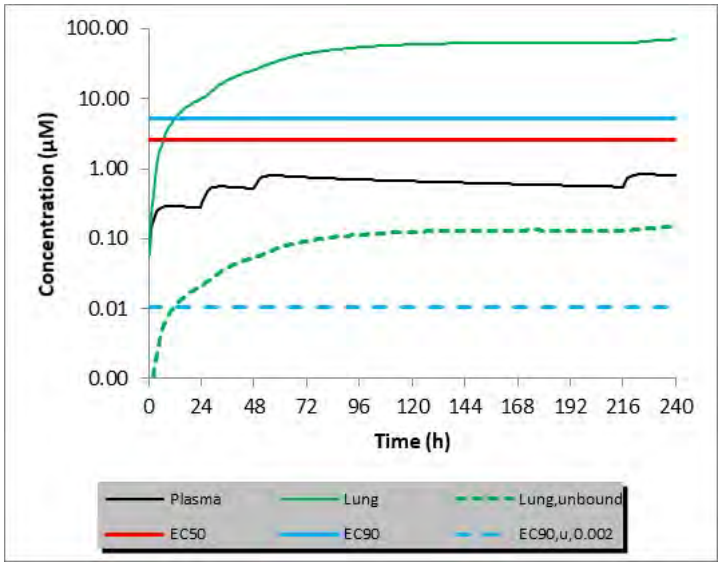
Tafenoquine inhibited SARS-CoV-2 replication and the yield of progeny virus in VERO E6 cells with $EC_{50/90s}$ for the latter endpoint of ~ 2.6/5.1 µM, and 4-fold greater potency than hydroxychloroquine (see Dow 2020 and the Investigator's Brochure for details on methodology used). Time of addition studies (head to head concentrations of 15 µM tafenoquine and hydroxychloroquine) were suggestive of either a more robust effect and/or a different mode of action for tafenoquine, with TQ inhibiting viral replication when added early in the viral replication cycle (Dow 2020).

Whole lung, lung unbound, and plasma concentrations were simulated following administration of the approved dose of TQ for malaria prophylaxis (200 mg on Days 1, 2, 3 and 10), using Certara's Simcyp model for tafenoquine (see Dow 2020 and the Investigator's Brochure for more details on methods, and the modeling assumptions made). Concentration time profiles over 10 and 60 days were plotted versus the in vitro EC_{50}, EC_{90}, and EC_{90u} values, with the latter calculated after adjustment for non-specific protein binding in the in vitro assay system (Dow 2020). As is evident from Figure 2, lung unbound concentrations exceed the $EC90_u$ for more than 60 days following administration of TQ.

Therefore, it is reasonable to hypothesize that the approved dose of TQ for malaria prophylaxis might reduce viral load in patients with COVID-19 disease, and thereby provide clinical benefit.

Figure 2 Predicted Tafenoquine Concentration-time Curves for Plasma, Lung, and Lung Unbound Following Administration of Tafenoquine

10 Days



60 Days

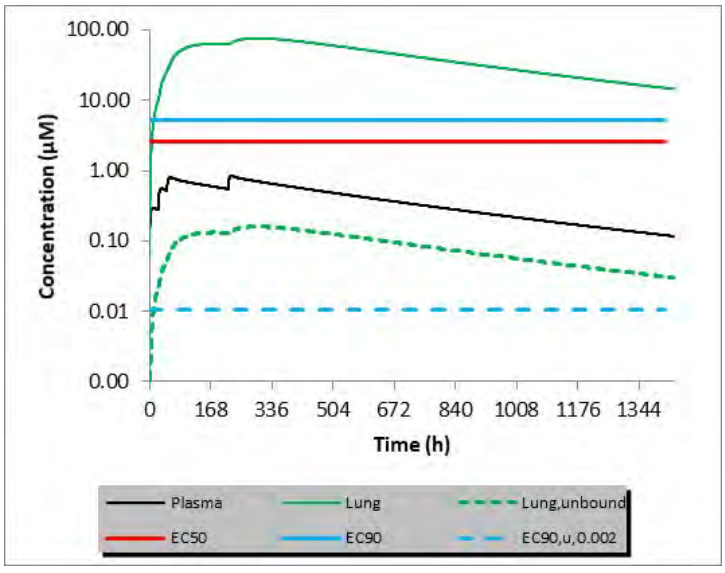


Figure 2: Predicted tafenoquine concentration-time curves for plasma, lung, and lung unbound following administration of tafenoquine at the approved dose for malaria prophylaxis (200 mg/day for three days followed by 200 mg one week later), in which the pH of lung tissue was assumed to be 6. The EC_{50}, EC_{90}, and EC_{90u} concentrations from the YR assay are indicated as horizontal lines across the figure.

4 STUDY OBJECTIVES

4.1 Primary

The primary objective is to determine if TQ increases the proportion of patients with clinical recovery from COVID-19 symptoms on Day 12 in patients with mild to moderate COVID-19 disease compared with placebo.

Clinical recovery is defined as:

- Temperature ≤ 37.7ºC [surface by infra-red or oral]
- Respiratory rate ≤ 24/minute on room air
- Shortness of breath is absent (Section 15.2.1)
- Cough is mild or absent on a patient-reported scale of absent, mild, moderate, and severe (Section 15.2.2)

4.2 Secondary

Secondary objectives include determining if TQ:

- Increases the proportion of patients with absence of detectable SARS-CoV-2 virus by RT-PCR at Day 12
- Increases the proportion of patients with absence of clinical symptoms by individual symptom at Day 12
- Decreases the hospitalization rate due to COVID-19 disease by Day 12
- Decreases the number of medical follow-up visits by Day 12

4.3 Exploratory

The exploratory objectives are to determine the time to maximum severity of COVID-19 symptoms and time to resolution of COVID-19 symptoms, with COVID-19 symptoms of interest being increased respiratory rate, fever, cough, and shortness of breath.

5 STUDY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary

- Proportion of patients with clinical recovery of COVID-19 symptoms at Day 12 [± 1 day]

5.1.2 Secondary

- Proportion of patients with negative SARS-CoV-2 RT-PCR on Day 12
- Hospitalization rates due to COVID-19 symptoms (excluding admittance only for administrative or observations purposes)
- Number of COVID-19-related medical follow up visits (Doctor's office or ER visit)
- Proportion of patients with COVID-19 symptoms at Day 12 by individual symptom

5.1.3 Exploratory

- Time to maximum severity of COVID-19 symptoms after start of treatment
- Time to resolution of COVID-19 symptoms including cough, fever, shortness of breath and elevated respiratory rate
- Proportion of individuals clinically recovered at Day 28 [± 1 day]

5.2 Safety Endpoints

- Adverse events (AEs) and serious adverse events (SAEs) events
- Vital signs (respiratory rate, temperature, heart rate, blood pressure, O_2 saturation)
- New clinical symptoms of COVID-19 disease not present at screening
- Clinical chemistry and hematology

6 STUDY DESIGN

6.1 Study Description

This study is a phase 2, multiple-dose, double-blind, placebo-controlled, study to assess the safety and efficacy of TQ in patients with mild to moderate COVID-19. Approximately 275 patients with COVID-19 will be enrolled with the goal of reaching 250 patients meeting the criteria for the mITT population at the end of the study (~125 TQ, ~125 placebo).

After signing the informed consent form, patients will have medical history taken and undergo laboratory testing including G6PD, FDA-authorized RT-PCR from nasopharyngeal [NP] swab specimens) to confirm presence or absence of SARS-CoV-2, pregnancy testing, hematology, blood chemistry, vital signs, O_2 saturation, physical exams, and will be assessed for COVID 19 symptoms including presence/severity of cough, presence/severity of shortness of breath, oral or skin temperature, and respiration rate. Patients who are eligible to participate in the study will be randomized in a 1:1 ratio to TQ or placebo within 2 days of the screening visit and will receive treatment on Day 1. Patients not meeting eligibility criteria will be considered a screen failure. Rescreening is permitted if first SARS-CoV-2 RT-PCR is negative, provided the patient has not been symptomatic for five days when the first dose of study medication is administered.

On Day 1, eligible patients will either return to the clinic or may have a telemedicine visit. Continued eligibility will be reviewed, and if still eligible, patients will be randomized and will receive and self-administer 200 mg TQ or matching placebo on Days 1, 2, 3, and 10 (each administration of drug will be within ± 1 day with the exception of the first dose). If the Day 1 visit is a telemedicine visit, the randomized blinded study drug will be couriered to the patient. Patients will be provided an oral thermometer to check and record their daily temperature and a home pulse oximeter to record their daily oxygen saturation. Patients will also be provided with an electronic study diary (eDiary) (loaded onto a device of their choosing) and be required to complete the eDiary entries from Day 1 through Day 12 [± 1 day]. Patients will record respiration rate, temperature, COVID-19 clinical signs including presence and severity of cough, respiration rate and shortness of breath, AEs, and concomitant medications in the electronic diary daily. They will also record study drug administrations in the diary to monitor compliance. Daily diary data will be automatically uploaded to the electronic data management system and will be reviewed daily by clinical staff.

Patients will be contacted by telephone or videoconferencing by designated study personnel on a daily basis to review AEs for severity by asking an open ended question, check for use of concomitant medications, and if there are new or worsening signs and symptoms of COVID-19 disease from Day 1 through Day 11 [± 1 day]. Telemedicine interviews will follow a script and information will be recorded in source documents. If a suspected SAE or worsening of signs and symptoms of COVID-19 are reported, a study physician will be contacted to determine if the patient needs additional support (clinic visit, medication, or emergency room visit). If the patient cannot be reached an individual from their emergency contact list will be contacted to determine if the patient has been hospitalized. Patients will return to clinic on Day 12 [± 1 day] for the assessments listed in Table 1. From Day 13 [± 1 day] through Day 28 [± 1 day], patients will be instructed to complete the eDiary and will have a final telemedicine call on Day 28 [± 1 day].

The schedule of study procedures is illustrated in Table 1.

6.1.1 Study Duration Per Patient

The total duration of the study will be up to 33 days for each patient, including 4 days for screening on Days -4 to -1, self-administration of study drug on Days 1, 2, 3, and 10, daily recording and remote collection of signs and symptoms from Day 1 through Day 11, an in-clinic visit on Day 12, and a telemedicine call on Day 28 ± day to assess AEs and clinical recovery.

6.1.2 Planned Number of Sites and Patients

The study will be conducted at multiple locations in the USA, Australia, or elsewhere as appropriate. Each site must have the capacity to conduct point of care COVID-19 RT-PCR test from NP swabs with a turn-around time no more than 48 hours. Sites must have access to point of care G6PD testing or be able to receive G6PD test result from an in-house or commercial laboratory within 48 hours. Sites must have pharmacy with capability to dispense study medication in secondary child-proof containers with appropriate labelling.

Approximately 275 patients with COVID-19 will be enrolled with the goal of reaching 250 patients meeting the mITT criteria at the end of the study.

6.1.3 Randomization

Eligible patients will be randomized at 1:1 ratio to receive TQ or placebo and stratified by site. Randomization will be performed through a centralized, web-based, validated system that automates the assignment of patients to treatment assignment. The randomization scheme will be reviewed and approved by the sponsor or designee. For study medication dispensation, the Investigator or designee will access the randomization system to determine which blinded study medication bottle the patients will be assigned.

6.2 Schedule of Study Assessments

Table 1 Schedule of Procedures

Procedure	Screening Day -4 to -1	Day 1	Day 1	Days 2 and 3 ± 1 day	Days 4 to 9	Day 10 ± 1 day	Day 11	Day 12 ± 1 day	Day 28 ± 1 day
Clinic Visit #	**1**	**If in clinic**	**If at home**					**2 or 3**	
Informed consent	X								
Eligibility criteria	X	X	X						
Pregnancy testing[1]	X							X	
Demography	X								
Medical history	X	updated	updated						
G6PD test	X								
Physical exam	X							X	
Vital signs[2]	X							X	
Clinical symptoms of COVID-19[3]									
Temperature[4]	X	X	Self-measured by patient daily and recorded in eDiary					X	
Respiration rate[5]	X	X	Self-measured by patient daily and recorded in eDiary						
Shortness of breath (severity scale) [6]	X	X	Self-reported by patient daily and recorded in eDiary					X	
Cough (severity scale) [7]	X	X	Self-reported by patient daily and recorded in eDiary					X	
Pulse oximetry for oxygen saturation	X	X	Self-measured by patient daily and recorded in eDiary					X	
Prior and concomitant medications[8]	X	updated	Recorded by clinician at telemedicine visit					X	Recorded by clinician at telemedicine visit
Adverse events			Self-reported by patient and recorded in eDiary, and recorded during telemedicine visit including severity and relationship to study drug, plus actions taken to treat AE or if drug discontinued					X	Recorded by clinician at telemedicine visit

Procedure	Screening Day -4 to -1	Day 1	Day 1	Days 2 and 3 ± 1 day	Days 4 to 9	Day 10 ± 1 day	Day 11	Day 12 ± 1 day	Day 28 ± 1 day
Clinic Visit #	**1**	**If in clinic**	**If at home**					**2 or 3**	
RT-PCR	X							X	
Hematology[9]	X							X	
Blood chemistry[10]	X							X	
Randomization		X	X						
Load eDiary to Patient Device, provide pulse ox device,thermometer, and instructions for use		X	X						
Dispense study drug[11]		X	X						
Study drug administration			X	Each day		X			
Medication compliance			eDiary	eDiary		eDiary			
Final drug accountability								X	

[1] A serum pregnancy test will be performed at screening and a urine or serum pregnancy test will be performed at Day 12.

[2]Vital signs include blood pressure and heart rate

[3] COVID-19 symptoms will be assessed by designated clinical staff at in-clinic visits and will be checked at home by the patients and reported by the patient in the electronic diary (eDiary). Once the data is recorded in the diary it will be uploaded to the study database for clinician review.

[4] Temperatures will be taken orally or on the skin surface and recorded in degrees Centigrade.

[5] After resting for 3 minutes the number of breaths will be taken over one minute.

[6] The severity of shortness of breath will be reported by the patient using the Modified Borg Scale for Grading the Severity of Dyspnea shown in Section 15.2.1.

[7] The severity of coughing will be reported by the patient using the Cough Severity Scale shown in Section 15.2.2.

[8] Prior medications used in the 14 days prior to the start of screening will be recorded.

[9] Hematology tests include: WBC count, absolute neutrophil count, RBC count hematocrit, hemoglobin, platelet count; C-reactive protein, INR, PT/PTT.

[10] Clinical chemistry tests include: BUN, creatinine, ALT and AST.

[11] Study drug will either be dispensed in the clinic, if the patient has a clinic visit on Day 1, or will be delivered by same day courier service to the patient at home on Day 1, after final eligibility has been determined the patient is randomized.

6.3 Rationale for Study Design and Selection of Dose

COVID-19 is a serious infectious disease that affected more than 11,190,000 people worldwide in 2020 (Worldometer 2020). There are currently no approved treatments for mild to moderate COVID-19 disease.

The dose of TQ selected for this study is consistent with the current label. Pharmacokinetic modeling suggests unbound lung concentrations at this dose exceed the EC_{90} of tafenoquine against SARS-CoV-2 in cell culture studies [see Section 3.4]. Double-blind procedures are included to reduce bias. A placebo control is included to demonstrate the effect of treatment with TQ.

7 SELECTION AND WITHDRAWAL OF PATIENTS

7.1 Inclusion Criteria

To be eligible to participate in this study, all of the following criteria must be met:

(1) Male or female, aged ≥18 years of age

(2) Laboratory confirmed infection with SARS-CoV-2 virus by an FDA-authorized RT-PCR test

(3) Able and willing to give written informed consent;

(4) Willing to keep a study diary from Study Day 1 to Day 12 [± 1 day] and have daily phone or videoconferences with study team personnel

(5) At least one of the following clinical symptoms of COVID-19 infection within the 4 days prior to and inclusive of the day of screening:

(i) Respiratory rate ≥ 24/min;

(ii) New cough or shortness of breath that has presented within the last 4 days; and/or

(iii) Fever ≥ 37.7ºC (oral or skin surface by infrared)

(6) Must agree not to enroll in another study of an investigational agent prior to completion of Day 28 of the study;

(7) Able to take ARAKODA or KODATEF according to Prescribing Information

(8) Have been symptomatic no longer than 5 days when the first dose of study medication is administered

(9) If female, agree to use an acceptable method of birth control from the time of consent through 56 days after the last dose of study drug

7.2 Exclusion Criteria

Patients are not permitted to enroll in the study if any of the following criteria is met:

(1) Have any of the contraindications for ARAKODA or KODATEF in the prescribing information (Section 15.1) including:
   a. G6PD deficiency
   b. Breastfeeding
   c. Psychotic disorder or current psychotic symptoms
   d. Known hypersensitivity reaction to TQ

(2) Evidence of severe or critical illness, defined by at least one of the following:
   a. Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥30 breaths per minute, heart rate ≥ 125 beats per minute, SpO_2 ≤93% on room air
   b. Respiratory failure defined based on resource utilization requiring at least one of the following:
      i. Endotracheal intubation and mechanical ventilation, oxygen delivered by high flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5),

noninvasive positive pressure ventilation, extracorporeal membrane oxygenation (ECMO), or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)

ii. Shock (defined by systolic blood pressure < 90 mmHg, or diastolic blood pressure <60 mmHg or requiring vasopressors)

iii. Multi-organ dysfunction/failure

(3) Any other clinically significant acute illness unrelated to COVID-19 within seven days prior to first study drug administration

(4) Receipt of any experimental treatment for COVID-19 (off-label, compassionate use, or study-related) within the 30 days prior to the time of the screening evaluation

(5) Any excluded concomitant medication as described in the ARAKODA package insert (Section 15.1)

(6) Any COVID-19 symptoms which, in the opinion of the investigator, is suggestive of possible requirement to hospitalize within 48 hours of enrollment

(7) Positive pregnancy test

(8) Have been symptomatic for more than five days when the first dose would be administered

7.3 Withdrawal Criteria

Patients are free to withdraw from the study at any time, without prejudice to their continued care.

Patients should have their Investigational Product withheld and continue to be followed for Safety per the protocol should any of the following events occur:

1. Patient develops an illness that would interfere with his/her continued participation.
2. Patient is noncompliant with the study procedures or medications in the opinion of the investigator. Patients who receive at least 1 dose of study drug should be followed for safety, if possible, until Day 28.
3. Patient takes prohibited concomitant medications as defined in this protocol.
4. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
5. The sponsor or a regulatory agency requests withdrawal of the patient.

Investigators should attempt to obtain information on patients in the case of withdrawal. For patients considered as lost to follow up, the investigator should make an effort (at least 1 phone call and 1 written message to the patient), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the patient, must be recorded in the source documents. The case report form (CRF) must document the primary reason for withdrawal.

If patients are hospitalized during the study period for anything other than being administratively registered in the hospital for observation, efforts should be made to continue the patient in the study

through Day 28. The Medical Monitor should assess the patient's ability to continue receiving study drug.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a patient in advance.

8 STUDY TREATMENTS

8.1 Identity of Investigational Products and Additional Products

Tafenoquine tablets for oral administration are pink, film-coated, capsule shaped tablets containing 125 mg of TQ 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).

Placebo tablets are identical in appearance and contain the excipients without the active substance (TQ).

8.2 Treatment(s) to be Administered

8.3 Packaging

The study drugs will be manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations.

Tafenoquine or matching placebo tablets will be conveyed to study sites by the sponsor in aluminum/aluminum blister cards with 8 tablets per blister card. The investigational pharmacist will remove tafenoquine or placebo tablets from the blisters and dispense 8 of each tablet into child-resistant HDPE bottles with labeling provided by the CRO.

8.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonization (ICH) guidelines and Good Clinical Practice (GCP) and GMP and will include any locally required statements.

8.5 Storage and Handling Procedures

The investigator (or designee) is responsible for the safe and proper storage of study drug at the site. Investigational medicinal product stored by the investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

The study drug should be stored at room temperature between 20 to 25ºC (or 68 to 77ºF). Appropriate storage conditions must be ensured and confirmed by completion of a temperature log (e.g. every working day).

In case an out of range storage temperature is noted, it must be immediately reported as per instructions contained in the Study Drug Handling Manual.

The investigator (or designee) will instruct the patient to store the study drug following the instructions on the label.

8.6 Drug Accountability

A Drug Accountability form will be used to record study drug dispensing and return information on a by patient basis and will serve as source documentation during the course of the study. Details of any study drug lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the

study site, or returned to the sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for the sponsor (or designee) to review.

The investigator (or designee) is responsible for retaining all used, unused, and partially used containers of study drug until returned or destroyed.

The investigator may assign some of the investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The investigator must ensure that the study drug is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired study drug must be reconciled and either destroyed at the site according to local laws, regulations, and the sponsor's SOPs or returned to the sponsor (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

8.7 Procedures for Monitoring Patient Compliance

Patients will self-administer study drug and record the administration in the patient diary. The study personnel will record this information after each phone call/videoconference.

At the Day 12 [± 1 day] visit, the patient must return all unused study drug to the site for destruction.

8.8 Study Restrictions

TQ is contraindicated in:

- Patients with G6PD deficiency or unknown G6PD status due to the risk of hemolytic anemia. Patients must be tested for G6PD deficiency prior to treatment with TQ
- Breastfeeding by a lactating woman when the infant is found to be G6PD deficient or if the G6PD status of the infant is unknown
- Patients with a history of psychotic disorders or current psychotic symptoms (i.e., hallucinations, delusions, and/or grossly disorganized behavior)
- Patients with known hypersensitivity reactions to tafenoquine, other 8-aminoquinolines, or any component of ARAKODA.

8.9 Important Administration Instructions

Patients will be instructed to:

- Administer study drug with food.
- Swallow the tablet(s) whole. Do not break, crush or chew the tablets.
- Complete the full course of study drug according to the schedule in Table 1.

8.10 Concomitant Medication(s)/treatment(s)

Any medications taken prior to administration of study drug will be recorded as prior medications. Any medications taken during the dosing period will be recorded as concomitant medications All

medications reported by the patient will be recorded on a source document and in the electronic case report form (eCRF).

8.10.1 Permitted Concomitant Treatments (Medications and Therapies)

The following concomitant medications are permitted during the study: over-the-counter cough, cold, and flu medication, and any medications routinely taken by the Patient other than prohibited medications as described in Section 8.10.2. If taking medications for a chronic condition (i.e., depression, diabetes, hypertension) patients must be on a stable dose and have been taking medication for at least one week.

8.10.2 Prohibited Concomitant Treatments (Medications and Therapies)

Prohibited concomitant medications include:

- Targeted COVID-19 therapeutics or therapies including remdesivir, dexamethasone, and convalescent plasma
- OCT2 and MATE substrates (e.g., dofetilide, metformin). If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction if needed based on approved product labeling of the coadministered drug

8.11 Blinding

All patients will be assigned a unique identifier and randomized to treatment using a randomization code provided by an IWRS system. Neither the patient nor the site staff will know to which treatment group the patient has been assigned.

8.11.1 Procedures for Maintaining and Breaking the Treatment Blind

8.11.1.1 Maintenance of Study Treatment Blind

The tablets are identical but will have been repackaged by the investigational pharmacist in child-proof HDPE bottles and labelled so that the blind is maintained.

8.11.1.2 Breaking the Treatment Blind in an Emergency Situation

All procedures taken during the unblinding process should be documented properly and reported to the Sponsor. The emergency unblinding process usually occurs in the following situations, but not limited to:

- In the case of an AE, where it is necessary for the Principal Investigator (PI) to know which treatment the patient is receiving so that the participant can be treated appropriately.
- The Data and Safety Monitoring Committee (DSMB) or other regulatory bodies (i.e., FDA, IRB) should have access to the unblinded data, when requested, or concerns during the conduct of the clinical research study.
- If someone not participating in the study ingests the study drug. For example, if a child in the patient's household takes the study drug, the blind may be broken to determine the appropriate treatment for the child.

- In the case of accidental overdose, the blind should be broken. Hemoglobin decline and methemoglobinemia may be encountered in an overdose with TQ. Treatment of overdosage consists of institution of appropriate symptomatic and/or supportive therapy.

The PI should follow the defined procedure to ensure the randomization code is broken only in accordance with the study protocol and per the Sponsor policy.

The PI may not break the blind except in an emergency situation as described above. In a nonemergency situation, the PI should contact the study sponsor's chief medical officer to obtain permission to break the blind.

Each site must create procedures to break the blind and maintain documentation regarding the any unblinding whether the blinding was due to an emergency situation or not.

9 STUDY PROCEDURES

9.1 Recruitment of Patients

Study recruitment will be accomplished through selection of qualified investigator(s)/institution(s) that are qualified by training and experience, and that are deemed to have adequate staff and resources to properly conduct the trial, and with access to the appropriate patient population. Prospective study subjects may be identified through an investigator's existing database, referral from an external clinician, or through new patients treated as part of an investigator's daily practice.

9.2 Screening Period

9.2.1 Informed Consent

At the first screening visit, candidates will meet with either the principal investigator or his/her designee and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the IRB. Patients will be given a copy of the signed informed consent form.

9.2.2 Week 1/Day -4 to Day -1 – In-Clinic

After signing informed consent, patients will have medical history taken and undergo laboratory testing including G6PD, FDA-authorized RT-PCR) from nasopharyngeal [NP] swab specimens), pregnancy testing, hematology, blood chemistry, vital signs, O_2 saturation, physical exams, and will be assessed for COVID 19 symptoms as described in Section 10.6. Patients who are eligible to participate in the study will be randomized in a 1:1 ratio to TQ or placebo within 2 days of the screening visit and will receive treatment on Day 1. Patients not meeting eligibility criteria will be considered a screen failure. Rescreening is permitted if first SARS-CoV-2 RT-PCR is negative, provided the patient has not been symptomatic for five days when the first dose of study medication is administered. Screening may be completed up to 48 hours prior to the Treatment Period.

9.3 Treatment Period

9.3.1 Week 1/Day 1 through Week 1/Day 3 (± 1 day for self-administration of study drug) – In-home

On Day 1, eligible patients will either return to the clinic or may have a telemedicine visit. Continued eligibility will be reviewed, and if eligible, patients will be randomized and will receive and self-administer 200 mg TQ or matching placebo on Days 1, 2, 3 ± 1 day. If the patient has an in clinic visit, s/he will be given sufficient study drug for the entire study. If the Day 1 visit is a telemedicine visit, the randomized blinded study drug will be sent via courier to the patient. Patients will be provided with an eDiary application (loaded onto a device of their choosing). The patient will self-administer study drug with food (per the label instructions [Section 15.1]) and record compliance in the eDiary. Patients will be provided an oral thermometer to check and record their daily temperature and a home pulse oximeter to record their daily oxygen saturation. Patients will record respiration rate, temperature, COVID-19 clinical signs including presence and severity of cough, respiration rate and shortness of breath, doctor's office and emergency room visits, AEs, and concomitant medications in the eDiary.

They will also record study drug administrations in the diary to monitor compliance. Daily diary data will be automatically uploaded to the electronic data management system and will be reviewed daily by clinical staff. Patients will be contacted by telephone or videoconferencing by designated study personnel on a daily basis to review AEs for severity by asking an open ended question, check for use of concomitant medications and more details such as dose, frequency, indication, and route of administration, and if there are new or worsening signs and symptoms of COVID-19 disease. Telephone interviews will follow a script and information will be recorded in source documents. If a suspected SAE or worsening of signs and symptoms of COVID-19 are reported, a study physician will be contacted to determine if the patient needs additional support (clinic visit, medication, or emergency room visit). If the patient cannot be reached an individual from their emergency contact list will be contacted to determine if the patient has been hospitalized.

9.3.2 Week 1/Day 4 through Week 2/Day 9 – In-home

Patients will record presence/severity of cough, presence/severity of shortness of breath, respiration rate, temperature, O_2 saturation, AEs, and concomitant medications in the eDiary. Daily telemedicine phone calls or videoconferences from study site personnel will be conducted as described directly above.

9.3.3 Week 2/Day 10 (± 1 day) – In-home

Study drug will be self-administered with food (per the label instructions [Section 15.1]) and compliance recorded. Patients will record presence/severity of cough, presence/severity of shortness of breath, respiration rate, temperature, O_2 saturation, AEs, and concomitant medications in the eDiary. The daily telemedicine phone call or videoconference with a study site staff member will be conducted as described directly above.

9.3.4 Week 2/Day 11 – In-home

Day 11 procedures will be the same as Days 4 through 9.

9.4 Follow-up Period

9.4.1 Week 2/Day 12 (± 1 day) – In-clinic

Assessments will be carried out according to the Schedule of Procedures (Table 1). Laboratory assessments will be conducted, including an FDA-authorized RT-PCR test for presence or absence of SARS-CoV-2. Physical exam, vital signs, pregnancy test, and clinical assessment of COVID-19 symptoms, including respiration rate, presence/severity of cough, presence/severity of shortness of breath, and oxygen saturation, will be recorded on a source document and entered into the eCRF. Patient eDiary data will be reviewed, and AEs will be assessed for severity and relationship to study drug and concomitant drug use will be recorded. All data will be recorded in a source document or eCRF.

9.4.2 Week 2/Day 13 to Week 4/Day 27 (± 1 day) – In-home

Patients will continue to enter data into the eDiary as done previously. The eDiary data will be reviewed by a clinical staff member, and if needed a telephone call will be made in the event that they patient reports worsening signs or symptoms of COVID-19 or a severe AE.

9.4.3 Week 4/Day 28 (± 1 day) – In-home

Patients will be contacted by telephone or videoconferencing by designated study personnel at Day 28 to review the status of any ongoing AEs at Visit 2, check for use of concomitant medications, and if there are new or worsening signs and symptoms of COVID-19 disease.

9.5 Withdrawal Early Termination Visit/ Unscheduled Visit

In the event a patient is withdrawn from treatment, they will be encouraged to continue in the study and undergo the follow-up assessments. Adverse event and concomitant medication reporting should be continued until the end of the study period.

10 ASSESSMENT OF SAFETY

10.1 Adverse Events

10.1.1 Definitions

10.1.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical (investigational product, whether or not related to the medical (investigational) product.

10.1.1.2 Serious Adverse Event

As provided by the ICH criteria, an SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
  Death represents an outcome and a SAE criterion, not an event term. The medical condition with the fatal outcome should be reported unless the cause of death is unknown, in which case the term "Death" is acceptable.
- A life-threatening adverse drug experience
  Any adverse drug experience that places the patient or patient, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
  (A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [e.g., life threatening adverse experience, important medical event].
  Initial and prolonged hospitalizations that do not meet this SAE criterion include those due to social and /or convenience reasons (e.g., lack of personal care at home, unable to transfer to non-acute facility), and those for preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner. For example, if a patient has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the preexisting condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined)
- A persistent or significant disability/incapacity (a substantial disruption of a person's ability to conduct normal life functions)

- A congenital anomaly/birth defect
- Other important medical event

NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

In addition, any laboratory result abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the CRF. Any abnormal laboratory result which is clinically significant (i.e., meets one or more of the following conditions) should be recorded as a single diagnosis on the AE page in the CRF:

- Accompanied by clinical symptoms
- Leads to permanent discontinuation of study medication
- Requires a change in concomitant therapy [e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant mediation, therapy or treatment].

This does not apply to abnormal laboratory results that do not meet the clinical significance criteria or those which are a result of an AE which has already been reported.

10.1.2 Assessing Adverse Events

When completing appropriate forms for reporting an AE, the Investigator will be asked to assess the AE as follows:

Seriousness of Adverse Event:

- Serious: The AE meets a criterion of the SAE definition.
- Not Serious: The AE does not meet a criterion of the SAE definition.

Severity of Adverse Event:

- Mild: No interference with functioning.
- Moderate: No significant interference with functioning.
- Severe: Significant interference with functioning.

Relationship of Adverse Event:

- Definitely: The adverse event follows a reasonable temporal sequence from the administration of the study medication; follows a known or expected response pattern to the study medication; is confirmed by improvement on stopping or reducing the dosage of the study medication (de-challenge) and reappearance of the event on repeat exposure (re-challenge); and cannot be reasonably explained by the patient's clinical state.
- Probably: The adverse event follows a reasonable temporal sequence from the administration of the study medication; follows a known or expected response pattern to

the study medication that is confirmed by improvement on de-challenge; and cannot be reasonably explained by the patient's clinical state.

- Possibly: The adverse event follows a reasonable temporal sequence from the administration of the study medication and follows a known or plausible response pattern to the study mediation but could readily have been produced by a number of other factors.
- Unlikely: A causal role of the study medication cannot be excluded, but the temporal relationship is atypical, and another plausible causal factor is present.
- Unrelated: The adverse event precedes the first administration of the study medication, or sufficient information exists to indicate that the etiology is clearly related to a cause other than the study medication.

Action Taken with Regard to Study Medication:

- Dose Not Changed
- Drug Interruption
- Drug Withdrawn
- Not Applicable
- Unknown

Other Action Taken:

- None
- Concomitant Therapy or Additional Treatment Given
- Therapeutic/Diagnostic Procedure
- Other

Outcome to Date:

- Recovered/Resolved: The patient recovered from the AE with no sequelae.
- Recovering/Resolving: The patient has not yet recovered from the AE, however the event is improving (follow-up of all serious AEs will be continued until the overall clinical outcome has been ascertained).
- Not Recovered/Not Resolved: The patient has not yet recovered from the AE; the event has not improved (follow-up of all serious AEs will be continued until the overall clinical outcome has been ascertained).
- Recovered/Resolved with Sequelae: The patient recovered from the AE with sequelae.
- Fatal: The patient's death was a result of the AE.
- Unknown: The outcome of the adverse event is unknown.

10.1.3 Reporting Adverse Events

The patient will be given instructions to record AEs on their eDiary and will be asked about AEs at the clinic visit on Day 12 and on the telephone visit at Day 28. In addition, the investigator should review AEs reported in the eDiary employed in the study.

When recording an AE, the investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source

documents should be consistent. Any discrepancies between the patient's own words on his/her own records (e.g., eDiary entry) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event CRF (including judgment of relationship to investigational device or study procedure) are described in the eCRF Completion Guidelines.

10.1.3.1 Data Safety Monitoring Board (DSMB)

An independent DSMB of external advisors will meet prior to the start of the study, and periodically during enrollment and follow-up and at trial end to review safety data. The Board will be blinded to patients' actual randomized group assignments but may request at any time that the blind be broken by the data center, 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 investigational product.

The subject will be given the opportunity to report AEs spontaneously. A general, nonleading, prompt will also be given at each study visit and during each study phone call to solicit AEs.

When recording an AE, the investigator should use the overall diagnosis or syndrome, using standard medical terminology, whenever possible, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (e.g., diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event eCRF (including the judgment of relationship to investigational product or study procedure) are described in the eCRF Completion Guidelines (CCGs).

10.1.3.2 Adverse Event and Serious Adverse Event Reporting Procedures

- Safety Contact Information:

Drug Safety Navigator (DSN)

Email: PVG@DrugSafetyNavigator.com

- AE Reporting:

AEs occurring (initial occurrence or a worsening of a pre-existing condition) after the subject signs the informed consent form and up to the final follow-up visit at Day 28 will be reported and included in the study database.

AEs will be reported on the AE CRF Form, and any related questions should be directed to DSN.

- SAE Reporting:

Any SAE experienced from the time the subject signs the informed consent up to the final follow-up visit at Day 28 will be reported to DSN as described below. Additionally, SAEs that occur after completion of the Follow-up period will also be reported to DSN if the Investigator considers the SAE related to study drug.

SAEs must be reported to DSN within 24 hours of the Investigator's (site's) awareness or notification of the event. To report the SAE, the site must complete the SAE Form for the study. This form is not part of the eCRF and will be provided separately to the Investigator by DSN. Initial and follow-up

SAE reports will be sent to DSN via email to PVG@DrugSafetyNavigator.com, and to the sponsor's Chief Medical Officer and to the Medical Monitor.

The SAE reporting should not be delayed, and the sites may call and provide the available SAE information within 24 hours of Investigator's awareness. A written SAE Form should be sent via email to PVG@DrugSafetyNavigator.com, as soon as possible.

The Investigators should make every effort to provide complete information on the SAE Form. At the minimum, the initial SAE report must contain the subject's identifiers, event term as known, SAE criterion and the Investigator's causality assessment. Additional information (or updates to the previously reported information) may be provided, as it becomes available through a follow-up SAE report.

The Investigator must continue to follow the subject until the SAE resolves, the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies. Within 24 hours of receipt of follow-up information, the Investigator must complete the SAE Form and submit any supporting documentation, as necessary (e.g., laboratory test reports, subject discharge summary, or autopsy reports) to DSN via email to PVG@DrugSafetyNavigator.com.

The Investigator is also required to submit SAE reports to the IRB in accordance with applicable requirements.

10.2 Pregnancy and Birth Control

All females should use an acceptable method of birth control (to be recorded on a source document and eCRF). Since a fetus would have an unknown G6PD status, TQ should not be used in pregnant women or in lactating mothers with infants of deficient or unknown G6PD status. If a patient becomes pregnant during the study or within 56 days of discontinuing study medication, the Investigator should report the pregnancy to Medical Monitor within 24 hours of being notified. CRO personnel will then forward the Exposure In Utero form to the Investigator for completion.

The patient should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Medical Monitor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

10.3 Overdose of Investigational Medicinal Product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the CRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (e.g., suicide attempt).

There is no experience of acute overdose with TQ, and management should be as clinically indicated. Hemolytic anemia and methemoglobinemia have been observed in clinical studies and are likely to be encountered in overdose.

10.4 Safety Signal Detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to TQ so that investigators, patients, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Medical Monitor or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the safety group representative.

TQ should be discontinued immediately, if signs of hemolysis (anemia, dark colored urine) or methemoglobinemia (cyanosis) develop during administration. Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing must be performed before administering TQ. Due to the limitations of G6PD tests, physicians need to be aware of residual risk of hemolysis, and adequate medical support and follow-up to manage hemolytic risk should be available. In clinical studies, declines in hemoglobin levels were reported in some G6PD-normal patients. Monitor patients for clinical signs or symptoms of hemolysis.

10.5 Laboratory Measurements

The following laboratory parameters will be measured:

- RT-PCR in NP swab
- Hematology: red blood cells (RBC), white blood cells (WBC) absolute neutrophil count, hematocrit, hemoglobin, platelets; C-reactive protein, international normalized ratio (INR), prothrombin time (PT)/ partial thromboplastin time (PTT)
- Blood chemistry: blood urea nitrogen (BUN), creatinine, alanine transaminase (ALT) and aspartate aminotransferase (AST)
- G6PD
- Pregnancy test (serum at screening and urine or serum at Day 12)

10.6 Other Measurements

10.6.1 Demographics

Patient demographics (gender, race, ethnicity, and age) will be recorded. Height and weight will be recorded.

10.6.2 Medical History

Medical history will be recorded including comorbid conditions and COVID-19 disease history.

10.6.3 Physical Examination

A physical examination of the oral cavity, head, eyes, ears, nose, and throat, cardiovascular system, lungs, abdomen, extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance. Abnormal findings will be recorded.

10.6.4 Vital Signs

Vital signs including blood pressure, heart rate, oral or skin temperature and breathing rate (respiratory rate), will be recorded at the screening and Day 12 clinic visit after sitting for a least 3 minutes. Temperature, respiratory rate taken over a one minute period and oxygen saturation will be recorded daily at by the patient at home in the eDiary. Patients will be provided an oral thermometer to check and record in the eDiary their daily temperature and a home pulse oximeter to record their daily oxygen saturation.

10.6.5 Hospitalizations

Hospitalization information will be recorded on a hospitalization form and included in the case book that captures the PIs assessment of the hospitalization including the reason for hospitalization, length of stay, and details of the hospital visit. Patients will be asked to provide hospital records. Patients will be followed up as described in Section 10.4.

10.6.6 Prior and Concomitant Medications

Medications including indication, start/stop date, dose, frequency, and route taken by the patient 14 days before the start of screening and for the duration of the follow-up period will be recorded on a source document and transcribed into an eCRF.

11 STUDY MANAGEMENT AND ADMINISTRATION

11.1 Adherence to Protocol

The investigator should not deviate from the protocol. However, the investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect patients from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or sponsor.

After implementation of such measure, the investigator must notify the sponsor within 24 hours and follow any local regulatory requirements.

11.2 Monitoring

Monitoring visits will be conducted by 60º Pharmaceuticals or designee according to applicable regulations and guidelines for GCP. The Investigator will permit the 60º Pharmaceuticals and/or designated representative(s) to make regular site visits during the study. The frequency of monitoring visits will be agreed upon by 60º Pharmaceuticals and/or designee. At each visit, the Investigator and staff will be expected to cooperate with 60º Pharmaceuticals or designee for the review and verification of protocol compliance, AE reporting, eCRFs, source documents, clinical supplies and inventory records, and any additional records as may have been previously arranged between the Investigator and 60º Pharmaceuticals or designated representative(s).

The Investigator and/or other designated study personnel are expected to contact the monitor of 60º Pharmaceuticals or designee as needed regarding study concerns and/or questions.

A Medical Monitor has been appointed by the Sponsor for the study. The Medical Monitor will be available for making recommendations to the investigator and the sponsor on the severity of any SAEs, and the relatedness to the study interventions. The Medical Monitor will also be responsible for tracking and assessing trends in the AEs reported.

11.2.1 Definition of Source Documents

It is the responsibility of the Investigator to collect and record all study data on source documents. The Investigator must provide access to source data/documents for study-related monitoring, audits, IRB/IEC review and regulatory inspection.

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies and/or printouts of eCRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x rays, laboratory results, printouts, pharmacy records, care records, or other printouts, completed scales, quality of life questionnaires, or video, for example. Source documents should be kept in a secure, limited access area. In cases where a device or instrument is the data originator (e.g., eDiary application) and data are automatically transmitted to the eCRF, then the eCRF is considered a source document.

Source documents that are computer generated and stored electronically must be printed for review by the monitor. Once printed, these copies should be signed and dated by the investigator and become a permanent part of the patient's source documents. The investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent. In some cases, electronic source documents will be monitored electronically by the sponsor or designee and will not be printed. The Investigator must ensure that the sponsor or designee has access to the electronic medical record for patients if such a system is used.

Electronic data records must be saved and stored as instructed by 60º Pharmaceuticals (or designee).

Patient-reported outcome (PRO) measures will be completed by each patient and will be collected electronically.

The data collection and database management system will be supplied by a vendor and will be compliant with regulations. All data collected including data collected from the ePRO diary will be uploaded to a central server database and will be sent electronically to 60º Pharmaceuticals (or designee).

11.2.2 Source Data Verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (e.g., patient files, recordings from automated instruments, x ray films, laboratory notes). All data reported on the CRF should be supported by source documents.

11.3 Data Handling

It is the Investigator's responsibility to ensure that data are collected and reported according to the study protocol. The Investigator will ensure the accuracy, completeness, and timeliness of the data reported on the eCRF and in all required reports. Efforts should be made to complete the eCRFs as soon after the scheduled visit as possible, and to have all eCRFs completed within 3 days after the Follow-up Visit.

Additionally, laboratory data will be received by Clinical Data Management from the appropriate clinical laboratory in electronic format. These data files may be merged with the clinical database.

11.3.1 Case Report Forms

Electronic CRFs will be produced according to protocol requirements, and access/training will be provided to all active sites in order for the Research Staff to record the data obtained on each patient during the study.

eCRFs must be completed for each patient enrolled (randomized) in the study. Data from patients that were screened but were ineligible for the study will not be included in the eCRFs, except that a Screen failure eCRF will be created to report the reason(s) that the patient was not eligible.

The CRFs must be kept up-to-date so that they always reflect the latest observations of the patients enrolled in the study. All records should be kept in conformance to applicable national laws and regulations.

11.3.2 Database Entry and Reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. Case Report form data are entered into the clinical database using independent, double data entry, with the exception of comment fields, which are verified by a second person. The data are entered into the electronic CRFs once and are subsequently verified if the study is performed using electronic data capture.
An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

11.3.3 Patient Screening and Enrollment Log/Patient Identification Code List

The patient's screening and enrollment will be recorded in the Patient Screening and Enrollment Log. The investigator will keep a Patient Identification Code list. This list remains with the investigator and is used for unambiguous identification of each patient.

The patient's consent and enrollment in the study must be recorded in the patient's medical record. These data should identify the study and document the dates of the patient's participation.

11.3.4 Quality Control and Quality Assurance

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Routine site monitoring;
- CRF review against source documents;
- Data management quality control checks;
- Statistical quality control checks;
- Continuous data acquisition and cleaning; and
- Quality control of final report.

A representative from 60º Pharmaceuticals and /or authorized representatives may conduct periodic audits of the clinical sites and study processes, including, but not limited to, the clinical database and the final report. The study may also be patient to inspection by regulatory authorities. The Investigator herby agrees to allow access to required patient records and other documentation and facilities related to the review and conduct of the study.

11.4 Study Termination

The study may be terminated at any time at the request of 60º Pharmaceuticals or the Investigator with proper and timely notification of all parties concerned. The IRB/IEC will be informed promptly and reasons for the termination or suspension will be provided by the Investigator, as specified by the applicable regulatory requirements. The study can be considered complete and/or terminated after 60º Pharmaceuticals has received the following data and materials:

- Laboratory findings, clinical data, and all special test results from screening through the end of the follow-up period
- CRFs properly completed (including all system or manually-generated edit checks properly answered and closed) by appropriate study personnel and signed by the Investigator
- Completed Drug Accountability Records
- Statement of outcome for each serious adverse event reported
- Approval/notification of protocols and protocol amendments from IRB/IEC as well as relevant health authorities (if applicable).

11.5 Archiving and Data Retention

An Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by patients. If the investigation is terminated, suspended, discontinued, or completed, the Investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under the U.S. Code of Federal Regulations 21 part 312.59.

An Investigator shall retain records required to be maintained under this part for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

60º Pharmaceuticals should inform the Investigator(s)/institutions(s) in writing of the need for record retention and should notify the Investigator(s)/institutions(s) in writing when the study related records are no longer needed.

Custody of the records may be transferred to another responsible part, acceptable to 60º Pharmaceuticals, who agrees to abide by the retention policies. Written notice of transfer must be submitted to 60º Pharmaceuticals. The Investigator must contact, and obtain the prior written permission of, 60º Pharmaceuticals prior to disposing of or so transferring any study records.

11.6 Audit and Inspection

The investigator will permit study related audits mandated by 60º Pharmaceuticals, after reasonable notice, and inspections by domestic or foreign regulatory authorities. The main purposes of an audit or inspection are to confirm that the rights and well-being of the patients enrolled have been protected, that enrolled patients (i.e., signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the study drug have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH GCP, and applicable regulatory requirements.
The investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the investigator will immediately inform 60º Pharmaceuticals (or designee).

11.7 Good Clinical Practice

This study will be conducted in compliance with the protocol, GCP as defined by the U.S. Code of Federal Regulations 21 parts 50, 56 and 312, Sponsor policies and procedures and all applicable state regulations.

Noncompliance with the protocol, ICH GCP, or local regulatory requirements by the investigator, institution, institution staff, or designees of the sponsor will lead to prompt action by 60º Pharmaceuticals to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

12 STATISTICAL METHODS

This section describes the planned statistical analyses in general terms. A complete description of the methodology will be specified in a statistical analysis plan (SAP), which will be finalized prior to database lock and unblinding. Any changes in the statistical methods described in this protocol that occur prior to database lock and unblinding will be documented in the statistical analysis plan and will not require a protocol amendment.

12.1 General Statistical Considerations

Statistical hypothesis testing will be performed at two sided alpha level of 0.05. For continuous variables, population size (N for sample size and n for available data), the mean, the standard deviation (SD), the median, the minimum and maximum values will be tabulated. For categorical variables, number and percentage in each category will be tabulated.

12.2 Analysis Populations for Analyses

Three patient populations will be defined:

- The modified Intention-to-Treat (mITT) population will include all patients who took at least one dose of study medication and had at least one post start of treatment assessment. The mITT population is analyzed as randomized, regardless of which treatment a patient received.
- Safety population: Any patient randomized and received any dose of study drug. Safety population is analyzed based on the actual treatment received.
- The PP population includes all mITT patients completing the Day 12 [± 1 day] in clinic visit without any major protocol deviations. Protocol deviation category (minor or major) will be determined prior to the database lock and unblinding.

Efficacy endpoints will be analyzed for the mITT population. Analyses of efficacy endpoints in the PP population will provide supportive evidence. Safety summaries will be based on the Safety population.

12.2.1 Patient Disposition

Study completion, number of patients in mITT, PP, Safety populations, and reasons for discontinuation for all randomized patients in the double-blind phase will be summarized for each treatment group by simple tabulation. Discontinuations by reason will be tabulated for each treatment group. The reasons that patients did not meet eligibility criteria (screen failures) will be provided in a listing.

12.2.2 Demography and Other Baseline Data

Demographic data will be tabulated by treatment group in the mITT population. Past and current medical history will be summarized by treatment group using the system organ class (SOC) as coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

12.2.3 Study Medication

Exposure and compliance will be presented as summary statistics by treatment group.

12.2.4 Prior/Concomitant Therapy

Prior/concomitant therapy will be summarized.

Any medications or therapy present before the first dose of study medication will be considered as prior medications. Concomitant medications (medications present while on study medication) will be recorded throughout the study and at early discontinuation. These medications will be coded using the WHO-drug dictionary. The number and percentage of patients from the safety population using prior or concomitant medications will be categorized by the WHO-drug class 4 name and presented for each treatment group. In any given category (e.g., drug category) a participant will be counted only once.

12.3 Planned Efficacy Analyses

12.3.1 Analysis of the Primary Efficacy Variable

The proportion of patients with clinical recovery at Day 12 will be analyzed using two methods: a 2x2 contingency table and logistic regression. The contingency table will provide unadjusted estimates of the proportions of patients with clinical recovery at Day 12. Copper-Pearson exact 95% confidence intervals around the recovery proportion within each treatment group will be provided. If 95% or more patients on the TQ arm have clinically recovered, then no logistic regression will be performed due to too few events then a Fisher's exact test will be used to compare treatment groups. However, if the rate is less than that then a logistic regression will be utilized. Treatment group will be the primary independent factor in the logistic regression. Additional covariates will be included in the model for every 10 events observed (eg, if at least 20 events then clinical site will be included, at least 30 events dichotomized number of symptoms (1-2 vs 3-4). Selection of additional covariates will be based on their relationship to the primary endpoint and correlation with other covariates. Patients who do not have a Day 12 visit due to hospitalization for COVID-19 symptoms will be considered treatment failures.

12.3.2 Other Efficacy Analyses

Dichotomous secondary endpoints will be analyzed in the same manner as the primary endpoint. The number of medical follow-up visits tabulated to determine if the endpoint can be considered continuous or ordinal. If the data are continuous the treatment groups will be compared by t-test. If the frequency distribution indicates few numbers of visits (eg 0, 1, 2, and 3 visits) then the analysis will use a chi-squared test to compare treatment groups. The methods for the conduct of the exploratory efficacy analyses will be provided in the SAP. Other *ad hoc* analyses not specified in the SAP may also be performed to further explore the data to aid in the design of future studies.

12.4 Planned Safety Analyses

12.4.1 Adverse Events

AEs will be coded using the most recent version of the Medical Dictionary of Regulatory Activities (MedDRA) preferred terms and will be grouped by system, organ, and class (SOC) designation. The incidence of new COVID-19 symptoms not present at screening will be reported separately from other AEs including the maximum severity and time of maximum severity relative to the start of investigational product. The severity, frequency, and relationship of AEs to investigational product will be presented by preferred term by SOC grouping. Listings of each individual AE including start

date, stop date, severity, relationship, outcome, and duration will be provided. Each AE (based on preferred terminology) will be counted once only for a given patient. If the same AE occurred on multiple occasions, the highest severity and relationship to investigational product will be assumed. Thus, study participants are not counted multiple times in a given numerator in the calculation of frequencies for a specific AE.

12.4.2 Laboratory Data

Clinical chemistry and hematology parameters will be summarized for absolute values and change from baseline (as appropriate) with descriptive statistics (means, medians, standard deviations, ranges).

12.4.3 Physical Examination

Physical examination findings will be coded using MedDRA preferred terms and SOC. The number and percentage of patients with abnormal finding physical examination will be provided by preferred term and SOC, and the individual data listing of abnormal findings will also be provided.

12.4.4 Vital Signs and Body Measurements

Data from vital signs will be summarized and listed, abnormal values will be flagged, and any other information collected will be listed. Data will be summarized by group using mean change from baseline and proportions of patients with values outside the normal range, and values that were clinically notable.

Summary tables and data listings of vital signs, including body temperature, blood pressure, pulse (heart rate), and breathing rate (respiratory rate), oxygen saturation will be provided for raw values and change from baseline (as appropriate).

12.5 Planned Interim Analysis and Data Monitoring

No interim analyses are planned.

12.6 Determination of Sample Size

The sample size calculation is based on the primary endpoint of recovery rate.

In a study of nonhospitalized patients with COVID-19 disease reported by Skipper (2020), placebo treated patients had resolution of clinical symptoms of COVID-19 by Day 14 in 70% of patients. Assuming an 85% clinical recovery rate in the TQ group and a 70% clinical recovery rate in the placebo group, sample sizes of 125 per treatment group will achieve 80% power with a two-sided alpha of 0.05 by logistic regression analysis.

13 ETHICS AND REGULATORY REQUIREMENTS

13.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

An Investigator shall assure that an IRB/IEC that complies with the requirements set forth in the U.S. Code of Federal Regulations 21 part 56 or requirements of the local regulatory authority (ex-USA) and will be responsible for the initial and continuing review and approval of the proposed clinical study. The Investigator shall also assure that he or she will promptly report to the IRB/IEC all changes in the research activity and all unanticipated problems involving risk to human patients or others, and that he or she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human patients.

All advertisements used in conjunction with this study must be reviewed and approved by 60º Pharmaceuticals prior to use and the IRB/IEC, if applicable. The IRB/IEC's approval will be documented in writing and sent to the Investigator. The Investigator will forward a copy of the ITB/IEC approval document to 60º Pharmaceuticals.

The Investigator will not begin the study until 60º Pharmaceuticals has authorized release of investigational drug product.

Any amendments to the protocol must be approved in writing by the IRB/IEC prior to implementation by the Investigator. However, any change to the protocol to eliminate an apparent immediate hazard to the patients may be implemented immediately, provided that the IRB/IEC is subsequently notified in accordance with code of federal regulations (CFR) Part 56.104C.

The Investigator will also provide the IRB/IEC with a current copy of the Investigator's Brochure at the start of the study, as well as an updated version of the Investigator's Brochure if revised during the study.

A progress report will be submitted by the Investigator to the IRB/IEC at intervals established by the IRB/IEC, and not less than annually. The Investigator will retain a copy of this report in the Investigator's Documentation File. After completion or termination of the study, the Investigator will submit a final report to the IRB/IEC. A copy of both reports will be sent to 60º Pharmaceuticals.

13.2 Informed Consent

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirement(s) [21 CFR Par 50] and should adhere to GCP regulations. Prior to the beginning of the study, the Investigator should have the IRB/IEC written approval of the written informed consent form and any other written information to be provided to patients.

The written informed consent form and any other written information to be provided to patients must be revised whenever important new information becomes available that may be relevant to the patient's consent. Any revised written informed consent form, and written information must receive the IRB/IEC approval in advance of use. The patient must be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. The communication of this information should be documented.

The Investigator, or a person designated by the Investigator, should fully inform the patient of all pertinent aspects of the study including the written information and the approval by the IRB/IEC. A copy shall be given to the patient.

All studies conducted at centers in the United States must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The patient may withdraw his/her consent to participate in the study at any time. A patient is considered as enrolled in the study when he/she has signed the Informed Consent form. A CRF must not be started, nor may any study specific procedure be performed for a given patient, without having obtained his/her written consent to participate in the study.

13.3 Patient Confidentiality

The Investigator, 60º Pharmaceuticals, and its representatives, agree to protect the privacy and confidentiality of the protected health information in accordance with applicable laws and regulations.

Patient medical information obtained by the study is confidential and disclosure to third parties other than those noted below is prohibited unless required by law. The Investigator shall retain all such information, and any other information designated by 60º Pharmaceuticals as confidential, or is otherwise of reasonably confidential nature, in confidence and shall not use such information for any purpose other than the performance of your obligations pursuant to your agreement with us, our affiliate or our contractor, as the case may be, without prior written authorization from 60º Pharmaceuticals.

At the patient's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection on request by representatives of regulatory authorities, 60º Pharmaceuticals, and the IRB(s)/IEC(s) if appropriate.

13.4 Protocol Amendments

With the exception of emergency situations, implementation of any change in the protocol that affects the safety of the patients, the scope of the investigation, or the scientific quality of the study will not be permitted until 60º Pharmaceuticals and the Investigator have approved the protocol amendment and the IRB/IEC responsible for review and approval of the study has reviewed and approved the protocol change.

Implementation of changes that do not affect the safety of the patients, the scope of the investigation, or the scientific quality of the study cannot be made until the protocol changes are reviewed and approved by 60º Pharmaceuticals and the Investigator. The IRB/IEC must be notified of these protocol changes.

13.5 Publications

The Investigator agrees that all data, calculations, interpretations, opinions and recommendations regarding the study shall be the sole and exclusive property of 60º Pharmaceuticals, and that 60º Pharmaceuticals may make any use thereof at its discretion without obligation to Investigator. The Investigator agrees to consider the results as information patient to confidential and use restrictions.

In the event that the study results are published in the scientific literature by 60º Pharmaceuticals, acknowledgment will be made to the Investigator(s) in the accepted style, as appropriate. The names of the Investigators or their representatives shall not be used by 60º Pharmaceuticals in publications, for advertising, for other commercial purposes, or otherwise, without appropriate written permission, unless required by law or government regulation.

Individual study center manuscript(s) for publication, text for talks, abstracts of papers, poster presentations, and similar material will be submitted to 60º Pharmaceuticals for review and comment prior to publication or disclosure. In order to ensure that 60º Pharmaceuticals will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to 60º Pharmaceuticals for review at least sixty (60º) days prior to submission for publication, public dissemination, or review by a third-party committee. 60º Pharmaceuticals will have sixty (60) days from receipt of such information to review and comment on and discuss the contents thereof with the Investigator. If 60º Pharmaceuticals requests, that the Investigator will remove any and all Confidential Information (other than Study results) prior to submitting or presenting the material. Upon the request of 60º Pharmaceuticals, Investigator will delay so submitting or presenting the materials for a further sixty (60) days to permit 60º Pharmaceuticals to take necessary actions to protect its Confidential Information, including the filing of patent applications.

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15 APPENDICES

15.1 Appendix A Prescribing Information ARAKODA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210607Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ARAKODA™ safely and effectively. See full prescribing information for ARAKODA™.

ARAKODA™ (tafenoquine) tablets, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
ARAKODA is an antimalarial indicated for the prophylaxis of malaria in patients aged 18 years and older. (1)

----------DOSAGE AND ADMINISTRATION----------
- All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing ARAKODA. (2.1)
- Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with ARAKODA. (2.1)

Regimen Name	Timing	Dosage
Loading regimen	For each of the 3 days before travel to a malarious area	200 mg (2 of the 100 mg tablets) once daily for 3 days
Maintenance regimen	While in the malarious area	200 mg (2 of the 100 mg tablets) once weekly – start 7 days after the last loading regimen dose
Terminal prophylaxis regimen	In the week following exit from the malarious area	200 mg (2 of the 100 mg tablets) one-time 7 days after the last maintenance dose

- Administer ARAKODA with food. (2.2)
- See full prescribing information for instructions on how to replace missed doses. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 100 mg of tafenoquine (3)

----------CONTRAINDICATIONS----------
- G6PD deficiency or unknown G6PD status (4)
- Breastfeeding by a lactating woman when the infant is found to be G6PD deficient or if G6PD status is unknown (4, 8.2)
- Patients with a history of psychotic disorders or current psychotic symptoms (4. 5.4)
- Known hypersensitivity reactions to tafenoquine, other 8-aminoquinolines, or any component of ARAKODA. (4)

----------WARNINGS AND PRECAUTIONS----------
- Hemolytic Anemia: G6PD testing must be performed before prescribing ARAKODA due to the risk of hemolytic anemia. Monitor patients for signs or symptoms of hemolysis. (5.1)
- G6PD Deficiency in Pregnancy or Lactation: ARAKODA may cause fetal harm when administered to a pregnant woman with a G6PD-deficient fetus. ARAKODA is not recommended during pregnancy. A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to ARAKODA through breast milk. Check infant's G6PD status before breastfeeding begins. (5.2, 8.1, 8.2)
- Methemoglobinemia: Asymptomatic elevations in blood methemoglobin have been observed. Initiate appropriate therapy if signs or symptoms of methemoglobinemia occur. (5. 3)
- Psychiatric Effects: Serious psychotic adverse reactions have been observed in patients with a history of psychosis or schizophrenia, at doses different from the approved dose. If psychotic symptoms (hallucinations, delusions, or grossly disorganized thinking or behavior) occur, consider discontinuation of ARAKODA therapy and, evaluation by a mental health professional as soon as possible. (5.4)
- Hypersensitivity Reactions: Serious hypersensitivity reactions have been observed with administration of ARAKODA. If hypersensitivity reactions occur, institute appropriate therapy. (5.5)
- Delayed Adverse Reactions: Due to the long half-life of ARAKODA (approximately 17 days), psychiatric effects, hemolytic anemia, methemoglobinemia, and hypersensitivity reactions may be delayed in onset and/or duration. (5.6, 12.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥1%) were: headache, dizziness, back pain, diarrhea, nausea, vomiting, , increased alanine aminotransferase (ALT), motion sickness, insomnia, depression, abnormal dreams, anxiety. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact 60 Degrees Pharmaceuticals at 1-888-834-0225 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
Avoid co-administration with drugs that are substrates of organic cation transporter-2 (OCT2) or multidrug and toxin extrusion (MATE) transporters (7.1)

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Advise women not to breastfeed a G6PD-deficient infant or infant with unknown G6PD status during treatment and for 3 months after the last dose of ARAKODA. (5.2, 8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ARAKODA is indicated for the prophylaxis of malaria in patients aged 18 years and older.

2 DOSAGE AND ADMINISTRATION

2.1 Tests to be Performed Prior to ARAKODA Dose Initiation

All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing ARAKODA *[see Contraindications (4), Warnings and Precautions (5.1)]*.

Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with ARAKODA *[see Use in Specific Populations (8.1 and 8.3)]*.

2.2 Recommended Dosage and Administration Instructions

The recommended dosage of ARAKODA is described in Table 1 below. ARAKODA can be administered for up to 6 months of continuous dosing.

Table 1: Recommended Dosage of ARAKODA in Patients (18 Years of Age and Older)

Regimen Name	**Timing**	**Dosage**
Loading regimen	For each of the 3 days before travel to a malarious area	200 mg (2 of the 100 mg tablets) once daily for 3 days
Maintenance regimen	While in the malarious area	200 mg (2 of the 100 mg tablets) once weekly – start 7 days after the last loading regimen dose
Terminal prophylaxis regimen	In the week following exit from the malarious area	200 mg (2 of the 100 mg tablets) taken one time, 7 days after the last maintenance dose

- Administer ARAKODA with food. *[see Clinical Pharmacology (12.3)]*.
- Swallow the tablet whole. Do not break, crush or chew the tablets.
- Complete the full course of ARAKODA including the loading dose and the terminal dose.

Table 2: How to Replace Missed Doses of ARAKODA

Dose(s) Missed	How to Replace Missed Dose(s):
1 Loading dose	1 dose of 200 mg (2 of the 100 mg tablets) so that a total of 3 daily loading doses have been taken. Begin maintenance dose 1 week after the last loading dose.
2 Loading doses	2 doses of 200 mg (2 of the 100 mg tablets) on 2 consecutive days so that a total of 3 daily loading doses have been taken. Begin maintenance dose 1 week after the last loading dose.
1 Maintenance (weekly) dose	1 dose of 200 mg (2 of the 100 mg tablets) on any day up to the time of the next scheduled weekly dose.
2 Maintenance (weekly) doses	1 dose of 200 mg (2 of the 100 mg tablets) on any day up to the time of the next scheduled weekly dose.
3 or more Maintenance (weekly) doses	2 doses of 200 mg (2 of the 100 mg tablets), taken as 200 mg (2 of the 100 mg tablets) once daily for 2 days up to the time of the next weekly dose.
Terminal prophylaxis dose	1 dose of 200 mg (2 of the 100 mg tablets) as soon as remembered.

3 DOSAGE FORMS AND STRENGTHS

ARAKODA tablets are dark pink, film-coated, capsule-shaped tablets debossed with 'TQ100' on one side containing 100 mg of tafenoquine.

4 CONTRAINDICATIONS

ARAKODA is contraindicated in:

- patients with G6PD deficiency or unknown G6PD status due to the risk of hemolytic anemia *[see Warnings and Precautions (5.2)]*.
- breastfeeding by a lactating woman when the infant is found to be G6PD deficient or if the G6PD status of the infant is unknown *[see Warnings and Precautions (5.3), Use in Specific Populations (8.2)]*.
- patients with a history of psychotic disorders or current psychotic symptoms (i.e., hallucinations, delusions, and/or grossly disorganized behavior) *[see Warnings and Precautions (5.4)]*
- patients with known hypersensitivity reactions to tafenoquine, other 8-aminoquinolines, or any component of ARAKODA *[see Warnings and Precautions* (*5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1. Hemolytic Anemia

Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing ARAKODA *[see Contraindications (4)]*. Due to the limitations with G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolytic risk should be available. Treatment with ARAKODA is contraindicated in patients with G6PD deficiency or unknown G6PD status *[see Contraindications (4)]*. In clinical trials, declines in hemoglobin levels were reported in some G6PD-normal patients *[see Adverse Reactions (6.1)]*. Monitor patients for clinical signs or symptoms of hemolysis *[see Warnings and Precautions (5.6)]*. Advise patients to discontinue ARAKODA and seek medical attention if signs of hemolysis occur.

5.2 G6PD Deficiency in Pregnancy and Lactation

Potential Harm to the Fetus

The use of ARAKODA during pregnancy may cause hemolytic anemia in a G6PD-deficient fetus. Even if a pregnant woman has normal levels of G6PD, the fetus could be G6PD deficient. Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception during treatment and for 3 months after the last dose of ARAKODA. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy *[see Use in Specific Populations (8.1 and 8.3)]*.

Potential Harm to the Breastfeeding Infant

A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to ARAKODA through breast milk. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown *[see Contraindications (4)]*. Advise the woman with a G6PD-deficient infant or if the G6PD status of the infant is unknown not to breastfeed during treatment with ARAKODA and for 3 months after the final dose *[see Use in Specific Populations (8.2)]*.

5.3 Methemoglobinemia

Asymptomatic elevations in methemoglobin have been observed in the clinical trials of ARAKODA *[see Adverse Reactions (6.1)]*. Institute appropriate therapy if signs or symptoms of methemoglobinemia occur *[see Warnings and Precautions (5.6)]*. Carefully monitor individuals with nicotinamide adenine dinucleotide (NADH)-dependent methemoglobin reductase deficiency. Advise patients to discontinue ARAKODA and seek medical attention if signs of methemoglobinemia occur.

5.4 Psychiatric Effects

In patients receiving ARAKODA in clinical trials, psychiatric adverse reactions included sleep disturbances (2.5%), depression/depressed mood (0.3%), and anxiety (0.2%) *[see Adverse*

Reactions (6.1)]. ARAKODA was discontinued in a subject with an adverse reaction of suicide attempt (0.1%). Subjects with a history of psychiatric disorders were excluded from three of five ARAKODA trials in which mefloquine was included as a comparator.

Psychosis was reported in three patients with a history of psychosis or schizophrenia who received tafenoquine doses (350 mg to 500 mg single dose, or 400 mg daily for 3 days) different from the approved ARAKODA regimen. Safety and effectiveness of ARAKODA have not been established at doses or regimens other than the approved regimen; use of ARAKODA at doses or regimens other than a 200-mg weekly dose is not approved by FDA.

ARAKODA is contraindicated in patients with a history of psychotic disorders or current psychotic symptoms *[see Contraindication (4)]*. If psychotic symptoms (hallucinations, delusions, or grossly disorganized thinking or behavior) occur, consider discontinuation of ARAKODA and prompt evaluation by a mental health professional as soon as possible. Other psychiatric symptoms, such as changes in mood, anxiety, insomnia, and nightmares, should be promptly evaluated by a medical professional if they are moderate and last more than three days or are severe *[see Warnings and Precautions (5.6)]*.

5.5 Hypersensitivity Reactions

Serious hypersensitivity reactions (e.g., angioedema and urticaria) have been observed with administration of tafenoquine. Hypersensitivity reactions have been reported in clinical trials of ARAKODA *[see Adverse Reactions (6.1)]*. Discontinue prophylaxis with ARAKODA and institute appropriate therapy if hypersensitivity reactions occur *[see Warnings and Precautions (5.6)]*. ARAKODA is contraindicated in patients who develop hypersensitivity to tafenoquine or any component of ARAKODA or other 8-aminoquinolines *[see Contraindications (4)]*.

5.6 Delayed Adverse Reactions, Including Hemolytic Anemia, Methemoglobinemia, Psychiatric Effects, and Hypersensitivity Reactions

Adverse reactions including hemolytic anemia, methemoglobinemia, psychiatric effects, and hypersensitivity reactions were reported with the use of ARAKODA or tafenoquine in clinical trials *[see Warnings and Precautions (5.1, 5.3, 5.4, 5.5)]*. Due to the long half-life of ARAKODA (approximately 17 days), psychiatric effects, hemolytic anemia, methemoglobinemia, and signs or symptoms of hypersensitivity reactions that may occur could be delayed in onset and/or duration. Advise patients to seek medical attention if signs of hypersensitivity occur *[see Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions observed with ARAKODA are discussed in detail in the Warnings and Precautions section:

- Hemolytic Anemia *[see Warnings and Precautions (5.2)]*
- Methemoglobinemia *[see Warnings and Precautions (5.3)]*
- Psychiatric Effects *[see Warnings and Precautions (5.4)]*

- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of tafenoquine was studied in clinical trials at various doses and regimens in 3,184 subjects. The recommended ARAKODA regimen was evaluated in 825 subjects in 5 controlled clinical trials (Trials 1, Trial 2, Trial 3, Trial 4 and Trial 5). The mean duration of exposure to ARAKODA in these five clinical trials was 21 weeks (range 10-29 weeks). Trial 1, 2 and 4 were conducted in healthy semi-immune volunteers in Ghana or Kenya and were placebo-controlled; a mefloquine arm was included in Trials 2 and 4 as a benchmark. Trial 3, an active comparator (mefloquine) controlled trial was conducted in healthy soldiers deployed in East Timor (Timor Leste). A placebo-controlled Trial 5 was conducted in healthy volunteers in the United States and United Kingdom. The mean age of the subjects included in the five trials was 29 years (range 17 to 69 years); 84% were male.

Adverse Reactions Reported with ARAKODA in Trial 3 and Pooled Trials 1, 2, 4, and 5

Adverse reactions occurring in ≥1% of subjects in the ARAKODA group in the placebo-controlled pooled Trials 1, 2, 3, and 4 are presented in Table 3.

Table 3: Selected Adverse Reactions Occurring in ≥1% of Subjects Receiving ARAKODA in Pooled Trials 1, 2, 4, and 5 (Non-Deployed Subjects))

Adverse Reaction	ARAKODA[2] (n=333) %	Placebo (n=295) %	Mefloquine[3] (n=147) %
Nervous system Disorders	35	34	47
Headache[4]	32	32	44
Dizziness[5]	5	3	10
Musculoskeletal and connective tissue disorders	27	26	37
Back pain	14	9	11
Gastrointestinal disorders	31	33	46
Diarrhea	5	3	1
Nausea	5	2	2
Vomiting	2	2	1
Investigations	8	7	11
Alanine Aminotransferase (ALT) increased/abnormal	4	2	3
Psychiatric disorders	2	1	2
Any sleep symptom[6]	1	1	0
Insomnia	1	1	0
Depression/depressed mood	1	0	0

[1] Trials 2 and 4 included mefloquine arm in addition to placebo
[2] ARAKODA was administered as 200 mg daily for 3 days, then 200 mg weekly
[3] Mefloquine was administered as 250 mg daily for 3 days, then 250 mg weekly
[4] Includes headache, sinus headache, migraine and tension headache.
[5] Includes dizziness and dizziness postural
[6] Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.

Adverse reactions occurring in ≥1% of subjects in the ARAKODA group in the active-control Trial 3 conducted in military personnel deployed to malaria endemic areas are presented in Table 4.

Table 4: Selected Adverse Reactions Occurring in ≥1% of Subjects Receiving ARAKODA in Trial 3 (Deployed Subjects)

Adverse Reaction	ARAKODA[1] (n=492) %	Mefloquine[2] (n=162) %
Nervous system Disorders	22	27
Headache[3]	15	19
Dizziness[4]	1	1
Ear and labyrinth Disorders	7	11
Motion sicknesss[5]	5	6
Musculoskeletal and connective tissue disorders	29	30
Back pain	14	15
Gastrointestinal disorders	36	41
Diarrhea	18	20
Nausea	7	9
Vomiting	5	6
Psychiatric disorders	5	4
Any sleep symptom[6]	4	4
Insomnia	2	1
Abnormal dreams[7]	2	2
Anxiety[8]	1	0

[1] ARAKODA was administered as 200 mg daily for 3 days, then 200 mg weekly
[2] Mefloquine was administered as 250 mg daily for 3 days, then 250 mg weekly
[3] Includes headache, sinus headache, migraine and tension headache.
[4] Includes dizziness and dizziness postural
[5] Includes motion sickness, vertigo and vertigo positional.
[6] Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.
[7] Includes abnormal dreams, nightmares
[8] Includes anxiety disorder, panic attack and stress.

Clinically Significant Adverse Reactions in Trials 1 to 5 (Overall Safety Population)

Clinically significant adverse reactions with ARAKODA (200 mg daily for 3 days, followed by 200 mg weekly) in Trials 1 to 5 (n= 825) are described below:

Ocular Adverse Reactions

Vortex keratopathy was reported in 21% to 93% of subjects receiving ARAKODA in the trials which included ophthalmic evaluations (Trials 3, 5, and Trial 6 (NCT # 01290601, an active-control trial in patients from Thailand with *P. vivax* malaria. The keratopathy did not result in any apparent functional visual changes and resolved within one year after drug cessation in all patients. Retinal abnormalities were noted in less than 1% of subjects receiving ARAKODA.

A total of 7 serious ocular adverse reactions (SARs) were reported in ARAKODA-treated subjects in the trials which included ophthalmic evaluations: 5 reports of keratopathy and two reports of retinal disorders.

Laboratory Abnormalities

Methemoglobinemia: Asymptomatic methemoglobin elevations were observed in 13% of subjects receiving ARAKODA.

Hemoglobin decrease: Hemoglobin decreases of ≥ 3 g/dL were observed in 2.3% of subjects receiving ARAKODA.

Adverse Reactions Reported in < 1% of Subjects Receiving ARAKODA in Trials 1 to 5

The following selected adverse reactions were reported in subjects receiving ARAKODA in Trials 1 to 5 at a rate of less than 1%.

Blood and lymphatic system disorders: hemolytic anemia, anemia, thrombocytopenia

Ear and labyrinth disorders: hyperacusis, Meniere's disease

Eye disorders: night blindness, photophobia, blurred vision, visual acuity reduced, visual impairment, vitreous floaters

Hepatobiliary disorders: hyperbilirubinemia, jaundice cholestatic

Immune system disorders: hypersensitivity

Investigations: blood bilirubin increased, blood creatinine increased, glomerular filtration rate decreased

Nervous system disorders: amnesia, coordination abnormal, hyperesthesia, hypoesthesia, somnolence, syncope, tremor, visual field defect

Psychiatric disorders: agitation, neurosis

Skin and subcutaneous tissue disorders: urticaria.

7 DRUG INTERACTIONS

7.1 Effect of ARAKODA on Organic Cation Transporter-2 (OCT2) and Multidrug and Toxin Extrusion (MATE) Substrates

The effect of coadministration of tafenoquine on the pharmacokinetics of OCT2 and MATE substrates in humans is unknown. However, in vitro observations suggest the potential for increased concentrations of these substrates *[see Clinical Pharmacology (12.3)]* which may increase the risk of toxicity of these drugs.

Avoid coadministration of ARAKODA with OCT2 and MATE substrates (e.g., dofetilide, metformin). If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction if needed based on approved product labeling of the coadministered drug.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The use of ARAKODA during pregnancy may cause hemolytic anemia in a fetus who is G6PD-deficient. Treatment with ARAKODA during pregnancy is not recommended. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy *[see Warnings and Precautions (5.2)]*. Available data with use of ARAKODA in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal studies, there were increased abortions, with and without maternal toxicity when tafenoquine was given orally to pregnant rabbits at and above doses equivalent to about 0.4 times the clinical exposure based on body surface area comparisons. No fetotoxicity was observed at doses about 1.5 times the clinical exposure (based on body surface area comparisons) in a similar study in rats.

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk:

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

Data

Animal Data:

Tafenoquine resulted in dose-related abortions when given orally to pregnant rabbits during organogenesis (Gestation Days 6 to 18), at doses of 7 mg/kg (about 0.4 times the clinical exposure based on body surface area comparisons) and above. Doses higher than 7 mg/kg were also associated with maternal toxicity (mortality and reduced body weight gain). In a similar study in rats, doses of 3, 10, or 30 mg/kg/day resulted in maternal toxicity (enlarged spleen, reduced body weight and reduced food intake) but no fetotoxicity at the high dose (about 1.5 times the clinical exposure based on body surface area comparisons). There was no evidence of malformations in either species. In a pre- and postnatal development study in rats, tafenoquine administered throughout pregnancy and lactation produced maternal toxicity and a reversible decrease in offspring body weight gain and decrease in motor activity at 18 mg/kg/day, which is equivalent to about 0.6 times the clinical dose based on body surface area comparisons.

8.2 Lactation

Risk Summary

A breastfed infant with G6PD deficiency is at risk for hemolytic anemia from exposure to ARAKODA. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown *[see Contraindications (4) and Clinical Considerations]*.

There is no information regarding the presence of ARAKODA in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. In a breastfed infant with normal G6PD, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARAKODA and any potential effects on the breastfed infant from ARAKODA or from the underlying maternal condition.

Clinical Considerations

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status in females of reproductive potential prior to initiating treatment with ARAKODA. *[see Dosage and Administration (2.2), Warnings and Precautions, (5.2), and Use in Specific Populations (8.1)]*.

Contraception

ARAKODA may cause hemolytic anemia in a G6PD-deficient fetus *[see Warnings and Precautions (5.2), Use in Specific Populations (8.1)]*. Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception for 3 months after the final dose of ARAKODA.

8.4 Pediatric Use

Safety and effectiveness of ARAKODA in pediatric patients have not been established.

8.5 Geriatric Use

Clinical trials of ARAKODA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

The pharmacokinetics of ARAKODA have not been studied in patients with renal impairment. If ARAKODA is administered to such patients, monitoring for adverse reactions associated with ARAKODA is needed *[see Warnings and Precautions (5), Adverse Reactions (6)]*.

8.7 Hepatic Impairment

The pharmacokinetics of ARAKODA have not been studied in patients with hepatic impairment. If ARAKODA is administered to such patients, monitoring for adverse reactions associated with ARAKODA is needed *[see Warnings and Precautions (5), Adverse Reactions (6)]*.

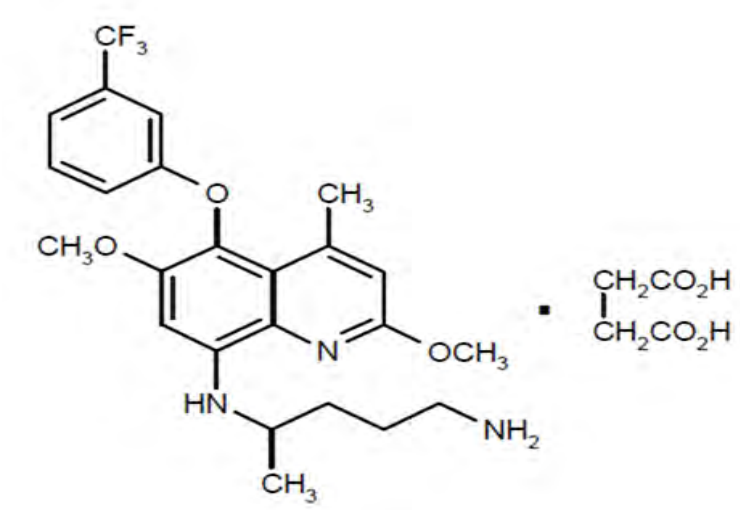
10 OVERDOSAGE

There were no reported cases of ARAKODA overdose. Hemoglobin decline and methemoglobinemia may be encountered in an overdose with ARAKODA. Treatment of overdosage consists of institution of appropriate symptomatic and/or supportive therapy.

11 DESCRIPTION

ARAKODA contains tafenoquine succinate, an antimalarial agent for oral administration. The structural formula of tafenoquine succinate is:

Figure 1: Tafenoquine Succinate Structure



The chemical name of tafenoquine succinate is (±)-8-[(4-amino-1-methylbutyl) amino]-2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl) phenoxy]quinoline succinate. The molecular formula of tafenoquine succinate is $C_{24}H_{28}F_3N_3O_3 \cdot C_4H_6O_4$ and its molecular weight is 581.6 as the succinate salt (463.49 as free base).

Each ARAKODA tablet contains 100 mg of tafenoquine (equivalent to 125.5 mg of tafenoquine succinate). Inactive ingredients include magnesium stearate, mannitol, and microcrystalline

cellulose. The tablet film coating inactive ingredients include: hypromellose, iron oxide red, macrogol/polyethylene glycol and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tafenoquine is an 8-aminoquinoline antimalarial drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of tafenoquine on the QT interval was evaluated in a study of healthy adult subjects. In this study, subjects received once daily 400 mg (2 times the approved recommended dosage) doses of tafenoquine for 3 days. The results suggest that the mean increase in the QTcF interval for tafenoquine is less than 20 msec.

12.3 Pharmacokinetics

Absorption

A food effect study was not conducted with the 100 mg ARAKODA tablet. In majority of the clinical trials, tafenoquine was administered under fed conditions. Table 4 provides the pharmacokinetics of tafenoquine following single dose administration of 200 mg ARAKODA (two 100-mg ARAKODA tablets) in 65 healthy adult subjects under fed conditions. In this study, ARAKODA was administered with a high-calorie, high-fat meal (approximately 1000 calories with 19% protein, 31% carbohydrate, and 50% fat).

Table 4. Mean (%CV) Pharmacokinetic Parameters of Tafenoquine Following Single Oral Administration of Two 100-mg ARAKODA Tablets Under Fed Conditions in Healthy Adult Subjects (N=65)

Parameter	Value
C_{max}	147 ng/mL (20.7%)[a]
T_{max}	14 hr (6 – 72 hr)[b]
AUC_{inf}	70 hr*mcg/mL (24.6%)[a, c]

[a] Coefficient of Variance (CV)
[b] Median and (Range)
[c] Plasma tafenoquine AUC_{inf} increased by 41% when tafenoquine was administered as an investigational capsule formulation with a high-calorie, high-fat meal compared with the fasted state.

Following administration of a single dose of tafenoquine orally under fasted conditions in healthy adult subjects, AUC and C_{max} increased dose proportionally over the dose range from 100 mg to 400 mg. When healthy adult subjects received once-weekly administrations of 200 mg tafenoquine orally for ten weeks without a loading dose under fasting conditions, the mean plasma accumulation ratio of tafenoquine was approximately 4.4.

Distribution

Tafenoquine is greater than 99.5% bound to protein in humans. The apparent volume of distribution of tafenoquine in healthy adult subjects is 2470 L [Inter-Individual Variability (IIV): 24.1 %].

Elimination

The apparent oral clearance of tafenoquine is approximately 4.2 L/hr (IIV: 23.6 %) in healthy adult subjects. The mean terminal half-life following administration of ARAKODA is approximately 16.5 days (range: 10.8 days to 27.3 days) in healthy adult subjects.

Metabolism

Negligible metabolism of tafenoquine was observed in vitro in human liver microsomes and hepatocytes. Following administration of tafenoquine orally, once daily for three days to healthy adult subjects, unchanged tafenoquine represented the only notable drug-related component in plasma at approximately 3 days following the first dose of tafenoquine.

Excretion

The full excretion profile of tafenoquine in humans is unknown.

Specific Populations

The pharmacokinetics of tafenoquine were not significantly impacted by age, sex, ethnicity, and body weight. The effect of renal or hepatic impairment on tafenoquine pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies

No clinically significant effects on the pharmacokinetics of substrates of cytochrome P450 isoenzymes (CYP)1A2 (caffeine), CYP2D6 (desipramine), CYP2C9 (flurbiprofen), or CYP3A4 (midazolam) were observed following coadministration with tafenoquine in healthy adult subjects.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

Tafenoquine inhibited metformin transport via human OCT2, MATE1 and MATE2-K transporters *[see Drug Interactions (7)]*.

Tafenoquine is not an inhibitor of human breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), Organic anion transporter 1/3 (OAT1 or OAT3), Organic anion transporting polypeptide 1B1/1B3 (OATP1B1 or OATP1B3) mediated transport at clinically relevant concentrations. Tafenoquine is also not a substrate of human OATP1B1 or OATP1B3 at clinically relevant concentrations. It is inconclusive as to whether tafenoquine is a substrate of P-gp and/or BCRP mediated transport.

12.4 Microbiology

Mechanism of Action

Tafenoquine, an 8-aminoquinoline antimalarial, is active against all the stages of *Plasmodium* species that include the hypnozoite (dormant stage) in the liver. Studies in vitro with the erythrocytic forms of *Plasmodium falciparum* suggest that tafenoquine may exert its effect by inhibiting hematin polymerization and inducing apoptotic like death of the parasite. In addition to its effect on the parasite, tafenoquine causes red blood cell shrinkage in vitro. The molecular target of tafenoquine is not known.

Antimicrobial activity

Tafenoquine is active against pre-erythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of *Plasmodium* species that include *P. falciparum* and *P. vivax.* The activity of tafenoquine against the pre-erythrocytic liver stages of the parasite, prevents the development of the erythrocytic forms of the parasite *[see Clinical Studies (14)]*.

Resistance

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

Studies with the erythrocytic forms of *P. falciparum* strains/isolates suggest a potential for cross-resistance with primaquine, an 8-aminoquinoline. Clinical relevance of such findings is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year oral carcinogenicity studies were conducted in rats and mice. Renal cell adenomas and carcinomas were increased in male rats at doses 1 mg/kg/day and above (0.5 times the clinical exposure based on AUC comparisons). Tafenoquine was not carcinogenic in mice. The relevance of these findings to a carcinogenic risk in humans is unclear.

Mutagenesis

Tafenoquine did not cause mutations or chromosomal damage in 2 definitive in vitro tests (bacterial mutation assay and mouse lymphoma L5178Y cell assay) or in an in vivo oral rat micronucleus test.

Impairment of Fertility
In a rat fertility study, tafenoquine was given orally at 1.5, 5, and 15 mg/kg/day (up to about 0.5 times the human dose based on body surface area comparisons) to males for at least 67 days, including 29 days prior to mating, and to females from 15 days prior to mating through early pregnancy. Tafenoquine resulted in reduced number of viable fetuses, implantation sites, and corpora lutea at 15 mg/kg in the presence of maternal toxicity (mortality, piloerection, rough coat, and reduced body weight).

14 CLINICAL STUDIES

Clinical Trials 1, 2, and 3

Three double-blind, randomized, controlled studies have been performed to evaluate the efficacy of ARAKODA.

Trial 1 (NCT #02491606) was a Phase IIb, placebo-controlled study conducted in Kenya, an area of holoendemic *P. falciparum* malaria. After taking a three-day presumptive course of halofantrine to eliminate any existing parasitemia, subjects were randomized into one of four groups (placebo and three different ARAKODA dosing groups; one group received 200 mg once daily for 3 days, then a maintenance regimen of weekly dose of 200 mg for 10-15 weeks). Sixty-one percent of subjects were male. The mean age was 32.4 years (range 17-55). Subjects were evaluated for parasitemia by weekly blood smears. Protective efficacy at 15 weeks was defined based on the reduced incidence of parasitemia during the prophylaxis phase relative to placebo. The results in the intention-to-treat population, which included all subjects who received three doses of halofantrine and were randomized, are shown in Table 5 below.

Table 5: Incidence of Parasitemia and Protective Efficacy of ARAKODA at 15 weeks for Trial 1

	Placebo	**ARAKODA[1]**
Number of subjects	62	61
Subjects free of parasitemia	5 (8.1%)	46 (75.4)
Subjects with parasitemia	54 (87.1%)	7 (11.5%)
Subjects with missing data	3 (4.8%)	8 (13.1%)
Protective efficacy [98.3% CI] [2]	–	73.3% [54.0%, 84.5%]

[1] 200 mg once daily for 3 days, then 200 mg weekly for 10-15 weeks
[2] Protective efficacy is reduced incidence of parasitemia relative to placebo (0: no protection; 1: full protection); CI: confidence interval. Bonferroni adjustment was used for multiple comparisons. Missing outcome was considered a failure due to parasitemia for this analysis.

Trial 2 (NCT #02488902) was a comparison of tafenoquine to placebo for prophylaxis in healthy semi-immune residents of a malarious region in Ghana. After treating existing parasitemia with quinine/doxycycline/primaquine, subjects were randomized into prophylactic groups including ARAKODA and placebo. Patients were administered a loading regimen of daily drug or placebo

for 3 days followed by a maintenance regimen of weekly drug or placebo for 12 weeks. For the ARAKODA and placebo groups, males were 65% of the total population. The mean age was 38.4 years and 53.5 years for males and females, respectively, as women in reproductive ages were excluded from the study. The mean weight was 55.4 kg and 47.5 kg for males and females, respectively. Subjects were evaluated for parasitemia by weekly blood smears. Parasitemia required a blood smear positive for asexual stage of *P. falciparum*. The incidence of parasitemia at week 12 for all randomized subjects who received at least one dose of ARAKODA or placebo is presented in Table 6 below.

Table 6: Incidence of Parasitemia and Protective Efficacy of ARAKODA at Week 12 for Trial 2

	Placebo	**ARAKODA**
Number of subjects	94	93
Subjects free of parasitemia	6 (6.4%)	68 (73.1%)
Subjects with parasitemia	86 (91.5%)	12 (12.9%)
Subjects with missing data	2 (2.1%)	13 (14.0%)
Protective efficacy [98.75% CI][2]	–	71.3% [55.8%, 81.4%]

[1] 200 mg once daily for 3 days, then 200 mg weekly for 12 weeks

[2] Protective efficacy is reduced incidence of parasitemia relative to placebo; CI: confidence interval. Bonferroni adjustment was used for multiple comparisons. Missing outcome was considered a failure due to parasitemia for this analysis.

Trial 3 compared ARAKODA with mefloquine for the prophylaxis of both *P. falciparum* and *P. vivax* malaria in healthy non-immune soldiers deployed to East Timor (now Timor-Leste). No subject developed malaria during the 26-week prophylactic phase. Subjects were exposed to *P. vivax* and there is a high likelihood that the study subjects were also exposed to *P. falciparum.* Since the precise degree of exposure to malaria in study subjects is unknown, this study provides only supportive evidence of efficacy.

Clinical Trial 7

In a randomized, double-blind, placebo-controlled trial (Trial 7) in healthy, non-immune volunteers, ARAKODA was shown to have prophylactic activity directed against blood-stage *P. falciparum* parasites. Twelve subjects received ARAKODA (200 mg once daily for 3 days, then 200 mg on 10 day) and 4 subjects received placebo. On Day 13, subjects were inoculated with erythrocytes containing viable *P. falciparum* parasites. Fifteen subjects (93.8%) were of white race. The mean age was 27.5 years (range 20-42). The mean body weight was 72.3 kg (range 56-97.7). The efficacy endpoint was parasitemia by Day 34; parasitemia was based on detection of *P. falciparum* 18S ribosomal DNA by real time polymerase chain reaction assay (PCR). There was a statistically significant difference in malaria incidence between the two groups; 4/4 (100%) subjects in the placebo group had detectable parasites from Day 17 compared to 0/12 (0%) subjects on ARAKODA were PCR negative at all visits ($p<0.0005$).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ARAKODA tablets contain 100 mg of tafenoquine (equivalent to 125.5 mg of tafenoquine succinate) and are dark pink, film-coated, capsule-shaped, and debossed with 'TQ100' on one side.

ARAKODA tablets are packed in polyamide aluminum and PVC formable laminate backed blisters with a peelable polyethylene terephthalate aluminum foil cover. Each blister card contains 8 tablets. Each carton contains 16 tablets (2 blister cards) (NDC 71475-257-01).

Storage

Store at 20°C to 25°C (68°F to 77°F). Temperature excursions are permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Dispense only in the original carton.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

G6PD Testing and Hemolytic Anemia

Inform patients of the need for testing for G6PD deficiency before starting ARAKODA. Advise patients on the symptoms of hemolytic anemia and instruct them to seek medical advice promptly if such symptoms occur. Patients should contact their health care provider if they have darker lips or urine as these may be signs of hemolysis or methemoglobinemia *[see Warnings and Precautions (5.1)]*.

Important Administration Instructions

- Advise patients to take ARAKODA with food.
- Advise patients to swallow the tablet whole and not to break, crush or chew it.
- Advise patients to complete the full course of ARAKODA including the loading dose, maintenance dose and terminal dose.

Potential Harm to the Fetus

Advise females of reproductive potential of the potential risk of ARAKODA to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.2) and Use in Specific Populations 8.1)]*.

Advise females of reproductive potential to avoid pregnancy or use effective contraception during treatment with ARAKODA and for 3 months after the final dose *[see Use in Specific Populations (8.3)]*.

Lactation
Advise women with a G6PD-deficient infant, or if they do not know the G6PD status of their infant, not to breastfeed during treatment with ARAKODA and for 3 months after the final dose *[see Contraindication (4), Warnings and Precautions (5.2), Use in Specific Populations (8.2)]*.

Methemoglobinemia
Inform patients that methemoglobinemia has occurred with ARAKODA. Advise patients on the symptoms of methemoglobinemia and instruct them to seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.3)]*.

Psychiatric Symptoms
Advise patients who experience hallucinations, delusions, or confused thinking while taking ARAKODA to seek medical attention as soon as possible. Other psychiatric symptoms, such as changes in mood, anxiety, insomnia, and nightmares, should be promptly evaluated by a medical professional if they last more than three days or severe *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions
Inform patients that hypersensitivity reactions have occurred with ARAKODA. Advise patients on the symptoms of hypersensitivity reactions and instruct them to seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.5)]*.

Manufactured For:
60 Degrees Pharmaceuticals LLC,
1025 Connecticut Avenue NW, Suite 1000,
Washington DC 20036

1217a

MEDICATION GUIDE
ARAKODA (AIR-uh-KOH-duh)
(tafenoquine)
tablets, for oral use

What is the most important information I should know about ARAKODA?
ARAKODA can cause serious side effects including:

- **Breakdown of red blood cells (hemolytic anemia).** See "**Do not take ARAKODA if you**:" ARAKODA can cause a breakdown of red blood cells (hemolysis) in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Your healthcare provider will test you for G6PD deficiency before you start taking ARAKODA. Signs of hemolytic anemia may not happen right away (delayed reaction).Tell your healthcare provider or get emergency medical help right away if you develop signs of hemolytic anemia which include darkening of the urine, dizziness, confusion, feeling tired, light-headedness, or shortness of breath, pale skin or yellowing of the skin and whites of the eyes.
- **Decrease of oxygen in your blood caused by a certain type of abnormal red blood cell (methemoglobinemia)**. Signs and symptoms of methemoglobinemia may not happen right away (delayed reaction). Get medical help right away if you have bluish coloring of the lips or skin, headache, fatigue, shortness of breath, or lack of energy.
- **Mental health (psychiatric) symptoms**. See "**Do not take ARAKODA if you**:" Sleep problems, depression, anxiety and psychosis have happened while taking ARAKODA. Psychiatric symptoms may not happen right away (delayed reaction). Get emergency medical help right away if you develop hallucinations (seeing or hearing things that are really not there), delusions (false or strange thoughts or beliefs), or if you get confused or have problems thinking while taking ARAKODA. Call your healthcare provider if you develop changes in your mood, anxiety, trouble sleeping (insomnia), or nightmares for 3 days or longer while taking ARAKODA.
- ARAKODA can have other serious side effects. See "**What are the possible side effects of ARAKODA?**"

What is ARAKODA?

- ARAKODA is a prescription medicine used to help prevent malaria in people 18 years of age and older.
- Malaria is a serious disease of the blood that is spread by infected mosquitos.
- It is not known if ARAKODA is safe and effective in children.

Do not take ARAKODA if you:

- have G6PD deficiency.
- are breastfeeding a child known to have G6PD deficiency or breastfeeding a child that has not been tested for G6PD deficiency.
- have a history of psychotic disorders, or you currently have psychotic symptoms including hallucinations (seeing or hearing things that are not really there), delusions (false or strange thoughts or beliefs), or disorganized thinking or behavior.
- are allergic to tafenoquine, other 8-aminoquinolines, or any of the ingredients in ARAKODA. See the end of this Medication Guide for a complete list of ingredients in ARAKODA.

Before taking ARAKODA, tell your health care provider about all your medical conditions, including if you:

- have nicotinamide adenine dinucleotide (NADH) reductase deficiency. People with NADH reductase deficiency have a higher risk for methemoglobinemia if they take ARAKODA.
- have or have had mental health problems.
- are pregnant or plan to become pregnant. ARAKODA can harm an unborn baby who has G6PD deficiency.
  - You should not become pregnant during treatment with ARAKODA.
  - Females who are able to become pregnant should use effective birth control (contraception) during treatment with ARAKODA. Talk with your healthcare provider about birth control methods that may be right for you.
  - Your healthcare provider may suggest you take a pregnancy test before you start taking ARAKODA. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with ARAKODA.
- are breastfeeding or plan to breastfeed. It is not known if ARAKODA passes into breast milk. See "**Do not take ARAKODA if you:**"
  - Your healthcare provider should check your child for G6PD deficiency before you start breastfeeding.
  - If you know your child has G6PD deficiency, do not breastfeed during treatment with ARAKODA and for 3 months after your last dose of ARAKODA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ARAKODA and other medicines may affect each other causing side effects.

How should I take ARAKODA?

- Take ARAKODA exactly as your healthcare provider tells you to take it.
- ARAKODA is given as 2 tablets that you will take together as a single dose. Each ARAKODA tablet has 100 mg of tafenoquine.
- You will **start taking ARAKODA** 3 days before you travel to a malaria area.

- Take 2 tablets, 1 time **each day for 3 days**.
- You will **continue to take ARAKODA** while you are in the malaria area.
  - Take 2 tablets, 1 time **each week**.
  - Start taking this dose of ARAKODA **7 days after the last dose of ARAKODA** that you took before your travel to the malaria area.
- You will **take your last dose of ARAKODA** after you leave the malaria area.
  - Take 2 tablets.
  - Take this dose of ARAKODA **7 days after the last dose of ARAKODA** that you took while you were in the malaria area.
- Take ARAKODA tablets whole. **Do not** break, crush, or chew the tablets before swallowing.
- Take ARAKODA with food.
- **It is important that you take the full course of treatment with ARAKODA**. **Do not** stop taking ARAKODA without first talking to your healthcare provider because the medicine may not work as well to prevent malaria.
- If you miss 1 or 2 daily doses of ARAKODA before your travel to the malaria area:
  - **1 daily dose**: take 2 tablets (missed dose), and then continue to take your daily dose of ARAKODA until you have taken a total of 3 daily doses before your travel to the malaria area. Start taking your weekly doses or ARAKODA 1 week after your last daily dose.
  - **2 daily doses**: take 2 tablets (missed dose), 1 time **each day for 2 days in a row (consecutive days)** so that you have taken a total of 3 daily doses before your travel to the malaria area. Start taking your weekly doses of ARAKODA 1 week after your last daily dose.
- If you miss any weekly doses of ARAKODA while you are in the malaria area:
  - **1 weekly dose**: take 2 tablets, 1 time on any day up to the time of your next scheduled weekly dose.
  - **2 weekly doses**: take 2 tablets, 1 time on any day before your next scheduled weekly dose.
  - **3 or more weekly doses**: take 2 tablets, 1 time **each day for 2 days** up to the time of your next scheduled weekly dose.
- If you miss taking your last dose of ARAKODA 7 days after the last dose of ARAKODA you took while you were in the malaria area, take this last dose of ARAKODA as soon as you remember.

What are the possible side effects of ARAKODA?
ARAKODA may cause serious side effects, including:

- See "**What is the most important information I should know about ARAKODA?**"
- **Allergic (hypersensitivity) reactions**. See "**Do not take ARAKODA if you**:"
  Allergic reactions can happen after you take ARAKODA. Signs and symptoms of an allergic reaction may not happen right away (delayed reaction). Get medical help right away if you have any signs or symptoms of an allergic reaction including:
  - swelling of the face, lips, tongue or throat
  - itching
  - trouble breathing or wheezing
  - vomiting
  - fainting and feeling lightheaded
  - rash
  - hives

The most common side effects of ARAKODA include: diarrhea, headache, back pain, nausea, vomiting, dizziness, increased liver enzyme levels in your blood, motion sickness, insomnia, depression, abnormal dreams and anxiety.
Other side effects of ARAKODA include eye problems. Some people who take ARAKODA can have a problem with the cornea of the eye called vortex keratopathy. This problem can be seen during an eye exam. Vortex keratopathy does not cause vision problems and will usually go away after you stop taking ARAKODA.

These are not all the possible side effects of ARAKODA.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to Sixty Degrees Pharmaceuticals, LLC at 1-888-834-0225.

How should I store ARAKODA?

- Store ARAKODA at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect tablets from moisture.

Keep ARAKODA and all medicines out of the reach of children.

General information about the safe and effective use of ARAKODA.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ARAKODA for a condition for which it was not prescribed. Do not give ARAKODA to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your pharmacist or healthcare provider for information about ARAKODA that is written for health professionals.

What are the ingredients in ARAKODA?
Active ingredient: tafenoquine succinate
Inactive ingredients: microcrystalline cellulose, mannitol, and magnesium stearate. The tablet film-coating contains the following inactive ingredients: hypromellose, iron oxide red, titanium dioxide, and macrogol/polyethylene glycol.

Manufactured for:

Sixty Degrees Pharmaceuticals, LLC
Washington, DC 20036
For more information, go to https://60degreespharma.com or call 1-888-834-0225.

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: August 2018


Arakoda™
(tafenoquine) tablets, for oral use
100 mg
16 (2x8) Unit Dose Tablets
Sixty Degrees Pharma
Rx only
NDC: 71475-257-01
KEEP OUT OF REACH OF CHILDREN
ATTENTION: Dispense the enclosed Medication Guide to each patient
Arakoda™
(tafenoquine) tablets, for oral use
100 mg
16 (2 x 8)
Unit Dose Tablets
Arakoda™
(tafenoquine) tablets, for oral use
100 mg
16 (2x8) Unit Dose Tablets
Sixty Degrees Pharma
EPO
Arakoda™
(tafenoquine) tablets, for oral use
100 mg
16 (2x8) Unit Dose Tablets
Sixty Degrees Pharma
Each tablet contains 100 mg tafenoquine (equivalent to 125.5 mg tafenoquine succinate). Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15 to 30°C (59 to 86°F).
Protect from moisture. Dispense only in the original carton.
See Prescribing Information for Dosage and Administration information.
Two blister packs are contained in each carton. Each blister pack contains eight 100 mg tablets of Arakoda™ (tafenoquine), for oral use.
Manufactured for:
60° Pharmaceuticals, LLC.
1025 Connecticut Ave., NW, Suite 1000
Washington DC 20036
Country of Origin: India
Arakoda™ (tafenoquine) tablets, for oral use
Sixty Degrees Pharma
For Positioning Only
Expiry: MMMYYYY
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/s/

EDWARD M COX
08/08/2018

15.2 Appendix B: Dyspnea and Cough Severity Scales

15.2.1 Rating of Perceived Dyspnea (RPD) Scale

Modified Borg Scale (MBS) during exercise or tasks. This scale allows you to rate the amount of shortness of breath you feel. The MBS goes from 0 to 10. A score of 0 means you have no shortness of breath at all (Crisafulli 2010).

Modified Borg Scale for Grading the Severity of Dyspnea

0	(Dyspnea) NONE
0.5	(Dyspnea) EXTREMELY MILD
1	(Dyspnea) VERY MILD
2	(Dyspnea) MILD
3	(Dyspnea) MODERATE
4	(Dyspnea) INTENSE
5	(Dyspnea) RATHER INTENSE
6	
7	(Dyspnea) VERY INTENSE
8	
9	(Dyspnea) ALMOST UNBEARABLE
10	(Dyspnea) UNBEARABLE

15.2.2 Cough Severity Scale

Rate your cough as one of the following:

1 – absent

2 – mild (may need a nonprescription medication)

3 – moderate (definitely needed a medication to control)

4 – severe (interfered with activities of daily living)