Australian Government
Department of Defence
Department of Veterans' Affairs

Departments of Defence and Veterans' Affairs Human Research Ethics Committee
CP3-7-038 Campbell Park Offices, PO Box 7912, Canberra BC ACT 2610

2016/188880

DDVA HREC/OUT/2018/R34682789

4 June 2018

Dr Mike Edstein
Australian Defence Force Malaria and Infectious Disease Institute

Copy: Dr Nguyen Ngoc San

Dear Dr Edstein

841-16 An open label study to assess the efficacy, safety and tolerability of pyronaridine-artesunate in the treatment of malaria infection cause by single of mixed species of *Plasomdium falciparum, P.vivax, or P. Malariae in Vietnam'*

The amendment to this project submitted on 29 May 2018 was approved out-of-session by the A/Chair of the Departments of Defence and Veterans' Affairs Human Research Ethics Committee (DDVA HREC) on 1 June 2018. The amendments are outlined in the attached Research Protocol Amendment Form.

You must forward a copy of this letter to all Principal Investigators and to your institution. Please note that all requirements of the original ethical approval for this project still apply.

Should you wish to discuss this matter, please contact the DDVA HREC Secretariat on (02) 6266 3807 or ddva.hrec@defence.gov.au.

Yours sincerely

Ms Terri Davis
Executive Officer

For
Mr Ian Tindall
A/Chair, Departments of Defence and Veterans' Affairs Human Research Ethics Committee

DEPARTMENTS OF DEFENCE AND VETERANS' AFFAIRS HUMAN RESEARCH ETHICS COMMITTEE

RESEARCH PROTOCOL AMENDMENT FORM

In the event that an approved research project requires amendment, this form must be submitted to the Departments of Defence and Veterans' Affairs Human Research Ethics Committee (DDVA HREC) by the Principal Investigator (PI).

An amendment **must not** be implemented until approval has been granted by the committee.

All completed forms are to be electronically submitted to ddva.hrec@defence.gov.au

Section 1: Project Details	
Protocol Number:	841-16
Project Title:	Efficacy and tolerability of pyronaridine-artesunate in treating uncomplicated mono-infections of falciparum, vivax and malaria or mixed infections in Vietnam'
Ethical approval date:	30 Nov 2016 - ADHREC 27 Mar 2017 – IRB QN IMPE 24 May 2018 – Vietnam MoH IRB in Biomedical Research
Ethical approval expiration date:	29 Nov 2019 - ADHREC 26 Mar 2021 - IRB QN IMPE 23 May 2021 - Vietnam MoH IRB in Biomedical Research
Date of amendment submission:	28 May 2018

Section 2: Investigator Details	
Name:	Dr Nguyen Ngoc San
Organisation (command/division):	Military Institute of Preventive Medicine, Vietnamese People's Army
Phone:	
Email:	MIHE VSPDQD [mp.mihe@gmail.com]

Section 3: Amendment Details

Explain the proposed/ intended changes *(may include changes in procedure, direction of project, source/manner of recruitment, number of participants or changes to research personnel)*

1. ADHREC 841-16 "Efficacy and tolerability of pyronaridine-artesunate in treating uncomplicated mono-infection of falciparum, vivax and malariae or mixed infections in Vietnam" was approved by ADHREC on 30 Nov 2016, with approval to conduct the research from 30 Nov 2016 to 29 Nov 2019. Several amendments to the ADHREC approved protocol VNPA-01 Version 1.0 15Jul2016 were requested by the Military Institute of Preventive Medicine (lead institute in Vietnam for the conduct of the study), Vysnova Partner Inc. USA and the US Naval Medical Research Center-Asia (sponsors of the study) and the Shin Poong Pharmaceutical Co. Ltd (the manufacturer of pyronaridine-artesunate "Pyramax®"). These

amendments led to the second version of the protocol (VNPA-01 Version 2.0 9Dec2017) which was submitted to the Vietnam Ministry of Health (MoH) National Institutional Review Board (IRB) in Biomedical Research on 10 May 2018. The revised protocol was approved by the IRB in Biomedical Research on 24 May 2018.

2. The major amendments to VNPA-01 Version 1.0 15Jul2016 which were incorporated into the IRB MoH approved protocol (VNPA-01 Version 2.0 9Dec2017) are as follows:

a. Change of study title from "Efficacy and tolerability of pyronaridine-artesunate in treating uncomplicated mono-infection of falciparum, vivax and malariae or mixed infections in Vietnam" to "An open label study to assess the efficacy, safety and tolerability of pyronaridine-artesunate in the treatment of malaria infection caused by single or mixed species of *Plasmodium falciparum*, *P. vivax*, or *P. malariae* in Vietnam."

b. Change of Principal Investigator from "Snr COL Nguyen Chinh Phong (MD, PhD)" to "Snr COL Nguyen Ngoc San (MD, PhD)." Snr COL Nguyen Chinh Phong has been posted to the Military Medicine Department of the Vietnam Ministry of Defense.

c. Removal of "LCDR Tyler Warkentien (MD, MPH), US NMRC-A, Singapore" who was posted back to the USA. LCDR Tyler Warkentien was replaced by two Project Officers representing the US Navy: LCDR Kristina St.Clair (DO, MTM&H) and LCDR Kimberly Edgel (PhD).

d. Amendments to the study synopsis and text are as follows:
   (1) Study Design: Duration of follow-up for participants treated for *P. falciparum*, *P. vivax* and mixed *Plasmodium* species to be the same at 42 days.
   (2) Drug Treatment: "Participants with mono-infections of *P. vivax* and *P. malariae* or mixed infections of *P. vivax* will receive the same course of pyronaridine-artesunate but primaquine treatment (14 day course) will not commence until day 28' changed to "Participants with mono-infections of *P. vivax* or mixed infections of *P. vivax* will also receive a standard 14-day course of primaquine treatment."
   (3) Study Sites: The addition of a second field site "Thuan An Commune in Dak Mil District" in the same province (Dak Nong).
   (4) Samples Size: Reduction in the number of malaria patients to be recruited from 150 to 120 patients.
   (5) Safety tests: The addition of hematology and biochemical tests before starting treatment (D0) and repeated on days 7 and 28 after commencing the 3-day course of Pyramax.
   (6) Inclusion Criteria:
      - Delete for adults the age limitation "up to 65 years old"
      - Add "Glucose-6-Phosphate Dehydrogenase (G6PD) normal patients with mono-infection of *P. vivax* or mixed infections of *P. vivax* will be treated with primaquine to kill liver hypnozoites."
   (7) Exclusion Criteria: addition of the following safety criterions:
      - Hematocrit <20%
      - Liver function test (AST/ALT levels) more than 2.5 times the upper limit of normal (ULN) range.

- Total bilirubin > 2 ULN.
- Shin Poong Pharmaceutical Co. Ltd requested the deletion from the exclusion criteria of "Known history or evidence of clinically significant disorders other than malaria such as Hepatitis B or C" as there is no evidence of either Hepatitis B or C adversely affecting the tolerability and efficacy of Pyramax in malaria patients. Such information is important for pharmacovigilance follow up.

(8) Addition of secondary objectives to the study synopsis as specified in the text of the protocol.

(9) Names changes: AMI to ADFMIDI (Australian Defence Force Malaria and Infectious Disease Institute) and ADHREC to DDVAHREC (Departments of Defence and Veterans' Affairs Human Research Ethics Committee).

(10) Reporting of adverse events of special interest has been added to the revised protocol. An adverse event of special interest (AESI) is an adverse event for which ongoing monitoring is appropriate within the context of the study. The study team is to take particular notice of symptoms/signs suggestive of clinical and biological signs of possible hepatotoxicity.

(11) The most popular and sensitive rapid diagnostic tests (RDTs) for malaria detection are based on antigens unique to *P. falciparum* [i.e., the histidine-rich proteins 2 (PfHRP2) and 3 (PfHRP3)]. Because RDTs play a critical role in informing malaria treatment and surveillance, particularly when blood smear microscopy is not available in the field, in the revised protocol we will also determine whether any participant is RDT negative for PfHRP2 and/or PfHRP3 but blood smear positive. This will provide prevalence data on the number of participants who carry *P. falciparum* parasites with the deletion of the histidine-rich proteins.

(12) Because of the continuous development of new genetic markers of parasite antimalarial drug resistance we have added to the revised protocol the provision to re-test the patient's samples for these potential new markers. To provide this opportunity the patient's de-identified blood spots will be kept for up to 10 years from the time of blood collection. To be allowed to do this in the participant information consent document approval is sought from the patient for the re-testing of their filter paper blood spots/parasite DNA for future new genetic markers of antimalarial drug resistance. The patient's samples collected under the revised protocol will not be used for genetic analysis of other diseases.

(13) Although malaria infection, particularly during the acute phase can cause adverse events such as nausea, abdominal pain, headache and dizziness, which often makes it difficult to distinguish disease effects from drug effects, in the amended protocol the study doctor will attempt to determine a causal association between the adverse event and the study drug.

(14) In addition to female patients of child-bearing age (10 to 55 years old) having a urine pregnancy test before enrolment in the study (D0), in the amended protocol they will also be asked to take another urine

pregnancy test on Day 28 and Day 42 after starting Pyramax treatment.

Reason for the changes *(include a comment on the impact on the research project and the participants at sites)*

The main reason for the changes were as follows:

a. The addition of safety checks (i.e., hematology and biochemistry measurements) to the protocol to ensure that the participants were suitable to be in the study and that Pyramax did not adversely affect their blood chemistries after starting treatment, particularly liver transaminases. No safety checks were incorporated in VNPA-01 Version 1.0 15Jul2016. With the addition of safety assessments the protocol title has been changed to "An open label study to assess the efficacy, safety and tolerability of pyronaridine-artesunate in the treatment of malaria infection caused by single or mixed species of *Plasmodium falciparum*, *P. vivax*, or *P. malariae* in Vietnam."
b. For participants with *P. vivax* malaria to be concurrently treated with both Pyramax and primaquine in accord with new MoH guidelines. In VNPA-01 Version 1.0 15Jul2016, primaquine treatment for *P. vivax* malaria was to commence at day 28 after starting Pyramax, so we would evaluate Pyramax by itself, without the presence of primaquine.
c. To follow all participants for 42 days after starting Pyramax treatment as opposed to following patients with *P. falciparum* and *P . vivax* for 42 days and 28 days, respectively, as specified in VNPA-01 Version 1.0 15Jul2016. The 42 days follow up for Pyramax plus primaquine would provide a better insight into the efficacy of the drug combination in preventing the first wave of relapses from the liver of participants.
d. The addition of a second neighbouring field site (Thuan An Commune in Dak Mil District) to enhance our chances of recruiting sufficient number of malaria patients over two years with malaria prevalence declining nationwide in Vietnam.
e. New PI and Project Officers added to the protocol.

Do these changes raise any ethical issues? ☐ Yes ☑ No

If yes, identify the ethical issues.

List all amended documents to be reviewed.

Document Title *(include version number, if applicable)* *Insert additional rows if required.*	**Version Date**
Amendments to the ADHREC 841-16 approved "Efficacy and tolerability of pyronaridine-artesunate in treating uncomplicated mono-infection of falciparum, vivax and malariae or mixed infections in Vietnam" (VNPA-01 Version 1.0 15Jul2016). In the revised protocol of VNPA-01 Version 1.0 15Jul2016 the amendments are highlighted in "yellow" and deleted information is struck out with a line through selected sentences, numbers and words.	VNPA-01 Version 1.0 15Jul2016
Protocol entitled, "An open label study to assess the efficacy, safety and tolerability of pyronaridine-artesunate in the treatment of malaria infection caused by single or mixed species	VNPA-01 Version 2.0 9Dec2017

of *Plasmodium falciparum, P. vivax,* or *P. malariae* in Vietnam." approved by Vietnam MoH IRB in Biomedical Research on 24 May 2018.	
Vietnam MOH IRB approval letter for Pyramax Study-VNPA-01 Version 2.0 9Dec2017	24 May 2018

Section 4: Participating Sites

Are all participating sites affected by this amendment? ☑ Yes ☐ No

If no, list all affected sites below. Insert additional rows if required.

Site *(Organisation)*	**State**

An amendment to an approved research protocol may also impact the individual research sites. The Commanding Officer (CO) at each affected site (named above) must be notified of the amendment by the PI to determine if the site is impacted. Final approval to implement an amendment at a site will be issued by that site's CO.

Section 5: Declaration

I confirm that this project is being conducted in keeping with the conditions of ethical approval. I confirm that the project is being conducted in compliance with the *National Statement on Ethical Conduct in Human Research.*

I confirm that I have not received any information in any form from anyone involved in the research to suggest this report does not accurately reflect the progress of the project.

	Michael D. Edstein
PI Signature	**Coordinating PI Printed Name**
Date: 29 May 2018	