

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210607Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



Food and Drug Administration  
Office of the Commissioner  
Office of Good Clinical Practice  
10903 New Hampshire Avenue, Bldg. 32, Rm. 5110  
Silver Spring, MD 20993-0002  
Telephone: 301-796-3707

**MEMORANDUM (Adult Ethics Consultation)**

Date: May 25, 2018

From: Kevin Prohaska, D.O., M.P.H., Captain (USPHS)  
Office of Good Clinical Practice, Office of the Commissioner

To: Yuliya Yasinskaya, M.D.  
Cross Discipline Team Leader, Division of Anti-Infective Products

Re: NDA 210607, Studies 033, 043, 045

**I. Materials Reviewed**

- 1) International Mefloquine Veterans Alliance, website details on tafenoquine; available at <https://imvalliance.org/?s=tafenoquine>
- 2) Australian Department of Defense “Tafenoquine FAQ’s”, available at [http://www.defence.gov.au/Health/HealthPortal/Malaria/AMI\\_research/tafenoquine-trials/FAQs.asp](http://www.defence.gov.au/Health/HealthPortal/Malaria/AMI_research/tafenoquine-trials/FAQs.asp)
- 3) Social Media from Quinism Foundation, available at <https://twitter.com/RemingtonNevin>
- 4) [REDACTED] (b) (4)
- 5) NDA 210607, Section 2.5 Clinical Overview
- 6) NDA 210607, Study 033, Appendix B, Informed Consent Document
- 7) NDA 210607, Study 033, Final Clinical Report
- 8) NDA 210607, Study 033, Case Report Form
- 9) NDA 210607, Study 043, Final Clinical Report
- 10) NDA 210607, Study 045, Final Clinical Report
- 11) NDA 210607, Section 2.7.3, Summary of Clinical Efficacy
- 12) NDA 210607, Section 2.7.4, Summary of Clinical Safety
- 13) NDA 210607, Section 2.7.6, Synopsis of Individual Studies
- 14) NDA 210607, Section 1.11.3, Clinical Information Amendment (Response to Information Request)
- 15) Army Regulation 70-25, “Use of Volunteers as Subjects of Research”, available at <http://usahec.contentdm.oclc.org/cdm/ref/collection/p16635coll11/id/789>
- 16) Emanuel EJ, et al, “What Makes Clinical Research Ethical?”, JAMA May 24/31, 2000: 2701-11
- 17) Belmont Report, available at <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html>
- 18) Council for International Organizations of Medical Sciences (CIOMS), “International Ethical Guidelines for Health-related Research Involving Humans”, dated 2016, available at <https://cioms.ch/shop/product/international-ethical-guidelines-for-health-related-research-involving-humans/>
- 19) International Conference on Harmonization (ICH) Guidance to Industry “E6 Good Clinical Practice”: <http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf>
- 20) “Integrated Addendum to ICH E6(2): Guideline for Good Clinical Practice,” Nov. 9, 2016, available at [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R2\\_Step\\_4.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4.pdf)
- 21) ICH Guidance E-10, “Choice of Control Group and Related Issues in Clinical Trials,” dated May 2001, available at

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073139.pdf>

- 22) ICH Guidance E8, "General Considerations for Clinical Trials", dated July 1997, available at <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/general-considerations-for-clinical-trials.html>
- 23) Emanuel EJ et al "What make clinical research in developing countries ethical? The benchmark of ethical research", J Infect Dis 2004; March 1;189(5); 930-7

## II. Background

On May 1, 2018, the Office of Good Clinical Practice (OGCP) within the Office of Medical Products and Tobacco (OMPT) received a consultative request from the Division of Anti-Infective Drug Products (DAIP), Center for Drug Evaluation and Research (CDER). The purpose of the request is for an OGCP ethical consultation to address the following concern related to NDA 210607:

*"Based on information submitted by the Applicant, did researchers respect and protect the rights and welfare of human research participants in Studies 033, 043 and 045, submitted under NDA 210607?"*

Additional background details provided in the consult are as follows:

*"The Division of Anti-Infective Products (DAIP) requests your expert opinion on the ethical considerations and conduct of studies conducted for the use of tafenoquine included in NDA 210607. This NDA is a resubmission after a refuse-to-file and has been granted priority review. The resubmission date is December 8, 2017. The proposed indication for tafenoquine is prophylaxis of malaria in adults for up to 6 months of continuous dosing. This NDA will be going to an Advisory Committee Meeting on July 26, 2018.*

1. **Study 033:** *One of the key studies (Study 033), enrolled soldiers deployed to combat areas. There are complaints about trial conduct for Study 033 in the public domain. Specifically, there are allegations of coercion and unethical informed consent procedures. Please assess whether the rights and welfare of human subjects participating in Study 033 were protected, based on the information provided by the Applicant.*
2. **Study 043 and Study 045:** *Two key studies were conducted in Kenya and Ghana (Study 043 and 045, respectively). Because allegations for Study 033 indirectly reference the entire tafenoquine development program, there may be concerns that populations living in potentially disadvantaged situations were exploited. Please assess whether the rights and welfare of human subjects participating in Study 043 and Study 045 were protected, based on the information provided by the Applicant.*

*Mefloquine was the comparator drug to tafenoquine for Study 033 and Study 045. Mefloquine is a drug related to tafenoquine which has Psychiatric and Neurologic Adverse Reactions in Boxed Warning, Contraindications, Warnings, Precautions, Adverse Reactions, and Overdosage. The neurologic and/or psychiatric adverse reactions associated with mefloquine exposure became apparent post-approval, with subsequent changes to the labeling. There are considerable concerns about mefloquine use in the public domain."*

Tafenoquine is a synthetic primaquine analogue developed by the US Army and SmithKline Beecham as a chemoprophylactic agent against all forms of malaria. An extensive preclinical and clinical development program for tafenoquine is contained in the NDA. For the purpose of this consult, I will focus my assessment on ethics of Studies 033, 043 and 045. All three studies were designed to evaluate the safety and efficacy of tafenoquine in the setting of an area in which malaria is endemic.

Malaria is a significant public health problem with an estimated 300 to 500 million infections and 1.5 to 2.7 million deaths per year worldwide. Four species of Plasmodia infect humans: *Plasmodium falciparum*, *P. Viva*, *P. Ovale*, and *P. Malariae*. Plasmodium Falciparum is considered the most significant public health concern due to its high morbidity and mortality. For non-immune individuals, medications such as chloroquine, pyrimethamine-sulfadoxine, mefloquine, and doxycycline have been used as prophylactic medication against malaria infections; however, resistant to these therapies is rapidly spreading. Hence, there is a significant public health need for the development of new therapies.

### **III. Study 033**

Study 033 was a randomized, double-blind, active controlled, study designed to evaluate the safety and effectiveness of tafenoquine compared to mefloquine for the prophylaxis of malaria in non-immune Australian soldiers (1<sup>st</sup> Battalion Royal Australian Regiment) deployed to East Timor. The objective of the study was to obtain safety and efficacy data on tafenoquine administered once weekly for 6 months. At the time the study was conducted, mefloquine was an approved drug product in Australia for the prevention of malaria and tafenoquine was an investigational drug product. Although mefloquine was considered by the Australian military as a second line drug for malaria prophylaxis, it was selected as the comparator for the trial because of its once weekly administration. The first line treatment was doxycycline which requires daily administration. The Study was conducted by the [Australian Army Malarial Institute](#) (AMI) and was supported by the U.S. Army and SmithKline Beecham Pharmaceuticals.

The final study report (completed in 2007) states the trial was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki and it was reviewed and approved by the Australian Defense Medical Ethics Committee (ADMEC) prior to study initiation. Additionally, the study report indicates the following steps were used to obtain informed consent (abbreviated, see section 3.3 “Ethics” of the final study report for full details):

- All potential subjects were collectively briefed on study details 4 to 6 weeks prior to deployment in groups of approximately 120. The study report indicates this was done in conjunction with other deployment related briefings.
- In the week prior to deployment, prospective subjects were given a copy of the consent document. The report indicates prospective subjects were permitted to seek external advice if they considered it necessary.
- At a subsequent meeting (typically the next day), prospective subjects were briefed on the details described in the consent document by the Principal Investigator or a co-investigator. The study report states effort was done to separate command elements, “to avoid any possibility of undue influence by senior officers.”

- Subjects then had a period of between 15 to 60 minutes to reflect on the information supplied, after which prospective subjects were interviewed in pairs (without any direct command relationship) by either the Principal Investigator or a co-investigator. During this meeting signed informed consent was obtained and witnessed by the paired colleague. Copies of the consent document were provided to subjects.
- The study report indicates that prospective subjects were encouraged to ask questions at every step.

In <sup>(b) (4)</sup> in the Australian military lodged a complaint with the Inspector General of the Australian Defense Force concerning what the complainant considered was unethical, unlawful, and negligent use mefloquine by the Australian military. Complete details about the allegations can be found in the report on the investigation done by the Inspector General (citation listed above). Amongst the complaints was an accusation that Study 033, conducted between 2000 and 2001 in Timor Leste, was unethical because it failed to comply with the National Health and Medical Research Council (NHMRC) “[National Guidelines](#)” for the conduct of clinical trials; prospective subjects were coerced to enroll; and prospective subjects were not adequately informed of the potential adverse effects associated with mefloquine (specifically its neurotoxic effects). Although not clear in the report, it also appears there was some concern that prospective informed consent was not obtained. The Australian National Guidelines for clinical research are similar to FDA’s regulations at 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards) and align with the international standards for Good Clinical Practice. <sup>(b) (4)</sup> also registered several complaints relative to issues unrelated to Study 033; however, for simplicity those complaints are not discussed in this review. It should be noted that <sup>(b) (4)</sup>

<sup>(b) (4)</sup> Details to support the accusation about Study 033 were apparently obtained by <sup>(b) (4)</sup> through interactions with individuals who participated in the trial through social networking such as Facebook. The accusations of the potential mistreatment of the troops resulted in significant media interest in Australia and a national government inquiry.

In response to the allegations, a formal inquiry was conducted by the Inspector General’s Office of the Australian Defense Force. The inquiry’s procedures included the gathering of relevant evidence, conducting and recording witness interviews, communications with individuals that participated in the research, an extensive review of the AMI trial files, consultation with subject matter experts, a review of the study report, and an assessment of the procedures followed by the Human Research Ethics Committee (equivalent to an IRB) that reviewed and approved the study.

In the Inspector General’s report, the AMI study records are described as very detailed and included background information on malaria; a summary of past research done on tafenoquine; an adequate justification for the trial; a data analysis plan; a detailed description of study procedures; a summary of the potential risks; a description of the informed consent process; and an informed consent document that included statements that consent is voluntary and refusal to participate will “*involve no penalty or loss of benefits*” and there will be “*no detriment to your medical care or your career.*” The study file also demonstrated the Study 033 was reviewed and approved by the Australian Defense Human Research Ethics Committee (ADHREC) on June 5, 2000 with a few minor amendments. Similarly, study records indicate that ADHREC conducted

three audits of the trial and found no significant problems “*other than one missing consent form.*” Hence, the Inspector General investigation determined that the accusation the study failed to comply with the National Guidelines was “unsubstantiated.”

As discussed above, Trial 033 was conducted in Australian Forces deployed to Timor Leste in 2000/2001. The inspector’s report indicates that the Commanding Officer of the forces to be deployed agreed to allow the trial to be conducted in his troops after consultation with experts from AMI. To facilitate the conduct of the trial, AMI deployed study staff to accompany the deployed Regiment to Timor Leste. The AMI staff assisted the Regimental Medical Officer with the pre-deployment medical briefs, provided medical support during the deployment, and were responsible for obtaining informed consent.

The accusation of coercion is based on [REDACTED] <sup>(b) (4)</sup> assertion (based on second hand information) that senior military leaders connected to the deployment to Timor Leste stated to the deploying troops during the pre-deployment period that participation in the trial was mandatory in order to deploy. During the investigation, the Inspector General interviewed several witnesses identified by the complainant and several witnesses identified through other means to include individuals from the Command Staff. Overall, the statements made by nearly all the witnesses (either in favor or against the accusations) were remarkable in that most stated they could not clearly recall the events and/or had vague recollections of the details. This is not unexpected, as the investigation and the interviews occurred nearly 15 years after the study. I defer the reader to the report for the full details related to the witness testimonies; however, in summary no witness could provide objective proof that anyone in a senior position stated that deployment was conditioned on participating in the trial. The one piece of information I found compelling, was a statement by a junior officer from the Command Group that stated had such an order been made he would have included it in his daily dairy. The diary apparently included details such as an order for soldiers to have wills, but nothing related to requiring solders to participate in the trial. Another witness also stated he had no memory of such an order and notes that had such an order been given he would have been the one responsible to implement it.

Given the nature of an order to compel someone to participate in research, I would expect a paper trail would exist to document the order, or in the very least, plans would have been made for the complex logistical efforts connected with leaving soldiers behind during a deployment. No such documentation appears to exist and those charged with carrying out such an order do not recall such statements being made or efforts connected to implementing such an order. My assessment of these testimonies is not meant to cast aspersions on the supporting witnesses. Details about who may have said what and when are often not well remembered after 15 years. My personal experience with military deployments suggests to me that the deploying troops could have easily conflated statements related to the large number of mandatory activities that must be completed during the pre-deployment period with statements about activities that are voluntary. It is also likely, the Commanding Officer’s support for the trial [REDACTED] <sup>(b) (4)</sup> could have been interpreted as a requirement to participate in the trial by some members of the Regiment. Although the Commanding Officer’s support for the study could be viewed as undue influence by some, the multi-tiered consent process (described above) was a reasonable way to minimize such influence. Similarly, the informed consent document for Study 033 includes several clearly written statements that consent was voluntary and refusal to participate would not

result in penalty. Based on the Inspector General's report, and the statements in the informed consent document, I see no evidence that soldiers were compelled to participate in Study 033. The Inspector General's report also determined that the allegation of coercion was not substantiated.

To minimize the potential for coercion and undue influence, the IG report notes the policies of the NHMRC includes a provision that where persons are in an unequal relationship, such as soldiers occupying subordinate positions in a hierarchical structured organization, additional attention is required by the ethics committee to be satisfied that consent is both adequately informed and voluntary, and that refusal to participate must not result in penalty. The investigation found through discussions with witnesses that the process for informing potential subjects of the trial included three medical briefs. The first briefing involved a large "bulk briefing" in which Study 033, and other issues related to pre-deployment were discussed. The second briefing involved small group discussions where questions could be answered. The last briefing involved two potential participants of equal rank and an AMI investigator reviewing the informed consent document. It was at this last briefing where consent forms were typically signed and witnessed. The report indicates that a Lieutenant Colonel [last name redacted in the report] stated this process for obtaining informed consent was followed in order to "*protect individuals from suffering any possible recourse from their decision not to enter the trial.*" In my opinion these additional steps to assure prospective troops were informed and that participation was voluntary seem reasonable.

The inspector's report indicates that 759 personnel underwent the recruitment process and 663 individuals agreed to participate. Ultimately, 654 individuals participated in the trial. The inspector general did not find any evidence that any individual was prevented from deploying to Timor Leste if they chose not to participate in Trial 033. In fact, evidence demonstrates that a substantial number of troops deployed without being enrolled in the trial. Individuals who declined to participate, were found ineligible, or withdrew from the study, were provided doxycycline as daily prophylaxes during the deployment. Overall, in my opinion, there does not appear to be any evidence to support the accusation that prospective subjects were coerced and that prospective informed consent may not have been obtained.

The accusation that soldiers were not adequately informed about the risks associated with the research relates to the complainant's belief that soldiers should have been informed about the potential neurotoxic risks associated with mefloquine to include permanent neurotoxic brain injury. In response to this accusation, the Inspector General reviewed the informed consent document for Study 033, reviewed the approved label and consumer information sheet for mefloquine that existed at the time the trial was conducted, and conferred with subject matter experts. Although a few deficiencies were identified in how the consent document described the known adverse event profile for mefloquine (e.g., it failed to include seizure and under estimated depression and anxiety), the Inspector General did not find the consent document materially incorrect. The report indicates that the potential for permanent neurotoxic effects with mefloquine were not known at the time and were not included in the approved product label. In summary, the Inspector General inquiry determined "*...the Inquiry is satisfied the trial participants were appropriately informed by the medical investigators of the potential side*

effects of both tafenoquine and mefloquine, and understood that participation in the trial was voluntary without detriment to deployment or future career.” I agree with this determination.

In summary, the Inspector General’s inquiry report states “...the evidence gathered and reviewed by the Inquiry indicates both trials were conducted ethically and lawfully by the AMI, in accordance with the National Guidelines issued by NHMRC and the TGA. The manner and use of both drugs in these circumstances was justified, reasonable, and consistent with the relevant health policy and guidance.” Based on the information contained in the Inspector General’s report, the final study report for Study 033, and details drawn from information on the web (e.g., Australian National Guideline), I believe the AMI researchers involved with Study 033 took appropriate steps to assure the rights and welfare of human research participants in Studies 033 were protected.

#### IV. Study 043

Study 043 was a randomized, placebo-controlled, double-blind, parallel group, single center study comparing weekly administration of tafenoquine to placebo for chemosuppression of *Plasmodium Falciparum* in approximately 250 subjects living in Western Kenya. Enrollment was limited to consenting Glucose-6-Phosphate Dehydrogenase (G<sub>6</sub>PD) normal, nonpregnant adults between 18 to 55 years of age in good health and living in Nyanza Province (an area in which *P. Falciparum* is holoendemic). Enrolled subjects were given 3 days of halofantrine<sup>1</sup> (250 mg daily) to eliminate any existing *Plasmodium* parasitemia, after which they were randomized to one of the following cohorts:

- Tafenoquine 400 mg daily for 3 days, followed by placebo for up to 10-15 weeks
- Tafenoquine 200 mg daily for 3 days, followed by tafenoquine 200 mg weekly for 10-15 weeks
- Tafenoquine 400 mg daily for 3 days, followed by tafenoquine 400 mg weekly for 10-15 weeks
- Placebo weekly

Subjects were followed weekly for safety and tolerability, and for *Plasmodium* parasitemia by repeated blood smears. The study plan also included frequent blood work to evaluate for safety and a final follow up visit for safety four weeks after the cessation of study medication. Subjects developing symptomatic malaria during the trial were withdrawn from the study and treated with standard curative treatments per local standards. An extensive array of preclinical and Phase 1 clinical studies supported the conduct of Study 043.

Overall, the final study reports states that tafenoquine was well tolerated and demonstrated good protection against *P. Falciparum*. Positive parasitemia was noted in 92% of the placebo treated subjects compared to a low of 9% for the high-dose tafenoquine cohort. Common adverse events include abdominal pain, diarrhea, constipation, headache, pharyngitis and dizziness. Two individuals experienced hemolytic anemia requiring treatment. I defer to the review division for a full analysis of the safety and efficacy of tafenoquine in Study 043.

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<sup>1</sup> Halofantrine is approved in the United States and Kenya for the treatment of parasitemia.

The original protocol justifies the use of placebo by noting that currently prophylaxis is not given to adult Kenyans permanently residing in the malaria endemic areas, except for pre-school children and pregnant women (both excluded from the trial); and that all subjects (including placebo cohort) will receive active antimalarial medication for at least part of the trial.

Additionally, the protocol states, the use of semi-immune individuals markedly decreases any risk of severe disease occurring in persons who develop parasitemia and individuals who are semi-immunes have a “real ethical advantage over non-immunes in chemosuppression studies because placebo and control groups can be justified in semi-immune groups.” Of note, the original protocol also includes evidence of close collaboration with Kenyan authorities and capacity building with Kenya Medical Research Institute. The study protocol indicates Study 043 was conducted under IND # (b) (4)

The final study report states that Study 043 was conducted in accordance with the Declaration of Helsinki; relevant local regulations; Kenya Medical Research Institute policies; and U.S. Army regulations (e.g., [Army Medical Research and Material Command regulation 70-25](#) (AR 70-25)). AR 70-25 outlines the roles and responsibilities of various individuals involved with the conduct of research and provides general and procedural guidance to assure the ethical conduct of research. Key amongst the protections described in AR 70-25 is a requirement that research supported or conducted by the Army be reviewed and approved by an Institutional Review Board prior to the start of the trial and prospective informed consent.

Study 043 was conducted in 1997 at the U.S. Army Medical Research Unit-Kenya in conjunction with Kenya Medical Research Institute (KEMRI). The study report indicates that the trial had two principle investigators (G. Dennis Shanks, M.D., LTC (U.A. Army) and Dr. A. J. Oloo M.B., ChB., M.Med. D.T. M.H. (KEMRI)). The final study report for Study 043 states that the protocol and the informed consent document were reviewed and approved by the Scientific Steering and Ethical Review Committee of KEMRI, the Scientific Review Committee of the Walter Reed Army Institute of Research, and the Human Use Review and Regulatory Affairs Division at USAMRMC. Additionally, the study report indicates that prospective informed consent was obtained from all subjects and a witness was involved when needed (e.g., illiterate individuals).

As described in the ethics consult request form, I was asked to opine on whether the rights and welfare of human subjects participating in Study 043 were protected. An assessment of this involves evaluating the overall ethical acceptability of Study 043. Determining the ethical acceptability of any study is a complex endeavor that is often limited by the details available and the framework used to assess the study. My analysis is limited to the details provided in the original protocol and the final study report. The framework I use is based on the principles outlined in the Belmont Report; the work by Emanuel et. al., and guidance developed by the International Conference on Harmonization (ICH) and the Council for International Organizations of Medical Sciences (CIOMS) [see above for citations]. The ethical acceptability of Study 043 can be assessed by evaluating the following factors; (1) Social Value; (2) Scientific Validity; (3) Fairness in subject selection; (4) Favorable risk to benefit analysis; (5) Oversight/Independent Review; (6) Respect for Persons; (7) Clinical Equipoise; and (8) Collaborative Partnership.

In clinical research, social value can be thought of as a requirement to have a research hypothesis that asks an important question, or said another way; the study evaluates a diagnostic or therapeutic intervention that could lead to an improvement in health and well-being. In my opinion, Study 043 has high social value given the development of multidrug resistant malaria and the need for alternative therapies to prevent and treat malaria.

Scientific validity requires that socially valuable research must be designed appropriately and conducted in a methodologically rigorous manner that will assure reliable and valid data. Scientifically unsound research on human subjects is ipso facto unethical in that it may expose subjects to risk for no useful purpose. Ethical requirements for clinical research dictate that a study should have the ability to meet its stated objective; otherwise any research-related risks that subjects are exposed to would be unjustified. As described in the final study report, Study 043 was extensively reviewed for scientific validity by multiple committees. In my opinion, Study 043 is scientifically valid.

Fair selection of subjects typically requires that the scientific goal of the study be the primary basis for determining the groups and individuals that will be enrolled in any given study. How this is accomplished is product specific. Additionally, fair selection of subjects recognizes that subject selection should endeavor to minimize risk and enhance benefit to individual subjects and society. Overall, in my opinion, subject selection for Study 043 was fair and appropriate efforts were made to minimize risk. Enrolling individuals at high risk of malaria is appropriate for a study designed to evaluate an investigational drug product for the chemoprophylaxis of malaria. Similarly, the study was appropriately limited to otherwise healthy, semi-immune, non-pregnant, G<sub>6</sub>PD normal individuals

The concept of a favorable risk to benefit ratio requires that, as much as possible, risks to subjects are minimized, the benefits are enhanced, and the potential risks be reasonable in relation to the potential benefits to the involved subjects and society. The concept of a favorable risk to benefit ratio embodies the ethical principles of non-maleficence and beneficence. Based on my review of the protocol and the final study report, the overall risk to benefit ratio appears to be reasonable. I also note that this principle is a standard that must be satisfied for approval by an IRB/Ethics Review Committee and for trials conducted under FDA's IND regulations.

Independent review typically means the use of an Institutional Review Board (IRB) or an Ethics Review Committee (ERC) to review and approve research prior to its initiation. The materials provided by the sponsor indicates that study 043 was reviewed and approved by a number of committees to include the Scientific Steering and Ethical Review Committee (b)(4), the Scientific Review Committee of the Walter Reed Army Institute of Research, and the Human Use Review and Regulatory Affairs Division at USAMRMC. In my opinion, the level of oversight and independent review appears adequate.

Respect for persons typically means the need to obtain consent from a fully informed individual that is free from coercion and undue influence. The informed consent process embodies the Belmont Report ethical principle of "respect for persons" by permitting them to make autonomous decisions. To be "informed" prospective subjects must be accurately informed of the purpose, methods, risks, benefits, and alternatives to research. Additionally, respect for

persons includes appropriate and considerate care throughout the entire length of time a subject is enrolled in the research. In my opinion, the details provided in the original protocol, the informed consent document, and the final study report indicates that the principle of respect for persons was satisfied. The sample informed consent document included all the basic elements of consent required under 21 CFR 50.25(a) and the protocol included provisions to assure the medical needs of subjects participating in the study were addressed throughout the trial and at its conclusion. The study report also indicates that subject voluntariness was assured by the use of a witness during the consent process and efforts were made to minimize coercion and undue influence (e.g., no payments was given for participation).

The principle of clinical equipoise in clinical research requires that there be genuine uncertainty in the expert medical community over which treatment arm in a clinical trial is best with respect to safety and/or efficacy. The concept of clinical equipoise embodies comparability of treatments and scientific uncertainty. That is, the two aspects of equipoise considered together imply reasonable comparability intrinsically among the arms of the trial and genuine uncertainty within the expert medical community about the preferred treatment. In my opinion., at the time Study 043 was reviewed and conducted there was sufficient uncertainty about the safety and efficacy of tafenoquine to support clinical equipoise between the actively treated cohorts.

The use of placebo in Study 043 is justified in the protocol on the premise that the standard of care in Kenya does not include the use of chemoprophylaxis against malaria in adult Kenyans permanently residing in the malaria endemic areas, except for pre-school children and pregnant women (both excluded from the trial); and that all subjects (including placebo cohort) will receive active antimalarial medication for at least part of the trial. Although helpful, in my opinion this alone would be considered inadequate justification if the circumstances of the research involved the potential for serious harm to the participants. ICH E 10, "[Choice of Control Group and Related Issues in Clinical Trials](#)", describes situations in which the use of placebo is ethically acceptable. As a rule, it is often considered unethical to have a placebo-only arm in a study for a serious condition when there are known effective treatments (or preventions as in this case). An exception to this rule would be a situation in which the known effective treatment has toxicity so severe that many individuals would be expected to refuse to receive it. In other situations, when there is no serious harm, it is generally considered ethical to ask patients to participate in a placebo-controlled trial, even if they may experience discomfort, providing the setting is noncoercive and patients are fully informed about available therapies. It is my understanding that the enrollment of semi-immune individuals drawn from an area in which malaria is holoendemic substantially mitigated the potential for serious harm; hence, in my opinion the use of placebo is ethically acceptable in this case. Finally, it should be noted that the protocol included provisions to treat any newly acquired parasitemia that may develop in any subject (including those treated with placebo) thus further mitigating the harms associated with participating in Study 043. It should be acknowledged, as discussed in the ICH E-10 guidance, that others may come to a different conclusion as to the ethics of using placebo in a given study; however, the oversight provided by the Kenyan authorities and the Kenyan Medical Research Institute suggests they had no concerns with the plan to use placebo in Study 043.

Finally, collaborative partnership in clinical research can be thought of as the combined efforts of the research team, the sponsor and the host country (or community) working collaboratively to

minimize the possibility of exploitation by ensuring the host country determines for itself whether the research is acceptable and responsive to the community's health problems. As described in the study report, Study 043 was done in collaboration with the Kenyan authorities and the Kenya Medical Research Institute. Details described in the study report suggests that the U.S. Department of Defense and the Kenya Medical Research Institute have a long history of working together and efforts were made to enhance capacity through the conduct of Study 043. Overall, the principle of collaborative partnership appears to have been satisfied.

In summary, based on my review of the information submitted by the Applicant, I believe subjects participating in Study 043 were ethically treated and their rights and welfare were adequately protected.

## V. Study 045

Study 045 was a randomized, placebo-controlled, double blind study designed to evaluate increasing doses of weekly tafenoquine for chemosuppression of *Plasmodium Falciparum* in approximately 530 semi-immune adults living in the Kassena-Nankana District of Northern Ghana. Enrollment was limited to healthy adult males (18 to 60 years) and females (50 to 60 years). The study builds on the experience from Study 043 and has many of the same design elements as Study 043 (e.g., conducted in highly endemic region with semi-immune individuals pre-treated with medications to eliminate pre-existing parasitemia). The exclusion criteria appear to be appropriately designed to minimize risk (e.g., G<sub>6</sub>PD deficiency, pregnancy, etc.). The study objectives were to, (1) to determine the chemosuppressive efficacy of weekly tafenoquine (dose range 25 to 200 mg) in preventing falciparum parasitemia compared to placebo, and secondarily to mefloquine, in subjects semi-immune to malaria; and (2) to establish the minimum effective prophylactic dose of weekly tafenoquine. Prior to randomization, all enrolled subjects were given 4 days of quinine (10 mg/kg TID), followed by 7 days of doxycycline (100 mg BID) and 14 days of primaquine (30 mg QD) to eliminate any existing *Plasmodium* parasitemia. Five days following this regimen subjects were randomized to one of the following cohorts:

- Tafenoquine 25 mg daily for 3 days, followed by tafenoquine 25 mg weekly for 12 weeks
- Tafenoquine 50 mg daily for 3 days, followed by tafenoquine 50 mg weekly for 12 weeks
- Tafenoquine 100 mg daily for 3 days, followed by tafenoquine 100 mg weekly for 12 weeks
- Tafenoquine 200 mg daily for 3 days, followed by tafenoquine 100 mg weekly for 12 weeks
- Mefloquine 250 mg daily for 3 days, followed by mefloquine 250 mg weekly for 12 weeks
- Placebo for 3 days followed by placebo weekly for 12 weeks

Randomization was based on clusters and subjects were equally randomized to each of the tafenoquine arms and the placebo arm; half as many were randomized to the mefloquine arm. The study plan also included frequent blood work to evaluate for safety and a final follow up visit for safety four weeks after the cessation of study medication. As described in the study materials, an extensive array of preclinical and human clinical studies supported the conduct of Study 045.

The study report and original protocol includes an adequate justification for the proposed trial and for the inclusion of individuals from Ghana. As discussed above for Study 043, malaria is a significant public health issue in many parts of Africa to include Ghana. The need for alternative

therapies, and alternative regimens of approved drugs, is needed to address the growing problem with multidrug resistance. Subjects developing symptomatic malaria during the trial were withdrawn from the study and treated with standard curative treatments per local standards.

The final study report indicates that the study was conducted with assistance from five different organizations from five countries. The study was conducted and coordinated from the (b) (4) (b) (4) in 1998. (b) (4) (b) (4) provided expertise in study supervision, laboratory support, and logistical support. Naval Medical Research Unit 3 (NAMRU-3) provided logistical support. The US Army Medical Material Development Activity (USAMMDA) funded the study and provided personnel to monitor the trial. Malaria Program, Naval Medical Research (NMRI) provided overall supervision and guidance for the study. SmithKline Beecham provided the study drug and case report forms. The principal investigator was Dr. Braden Hale MD., MPH (U.S. NAMRU-3) and the co-investigators included a number of individuals from (b) (4)

The final study report states the study was conducted “in accordance with code 32 of Federal Regulations Part 219 (Protection of Human Subjects), Department of Defense (DOD) Directive 3216.2 (Protection of Human Subjects in DOD-Supported Research), Secretary of the Navy (SECNAVINST) 3900.39B (Protection of Human Subjects), Naval Medical Command Instruction (NAVCOMINST) 6710.4 (Use of Investigational Agents in Human Beings), Naval Medical Research and Development Command (NMRDCINST) 3900.2 (Protection of Human Research Volunteers from Research Risks), and Secretary of the Navy Instructions (SECNAVINST) 5370.2H (Standards of Conduct) and USAMRMC reg. 70-25 (use of volunteers as subjects of research). Existing policies of NHRC and the Ministry of Health, Republic of Ghana were also followed.

The U.S. Department of Defense (DoD) human subject regulations are analogous to the Department of Health and Human Services regulations for human subject protections (i.e., 45 CFR part 46) and FDA regulations at 21 CFR parts 50 and 56. Additionally, the DoD regulations are in line with international standards for good clinical practice that, among other things, require clinical trials to be reviewed and approved by an ethics review board and prospective informed consent be obtained. Details outlined in the study report indicates Study 045 was approved by the Ministry of Health of the Republic of Ghana; multiple scientific and ethical review committees (b) (4) the Scientific Review Committee of USAMMDA; and the Human Review and Regulatory Affairs Division at USAMRC. Similarly, the final study report indicates that prospective informed consent was obtained from all subjects prior to enrollment.

Overall, the final study report indicates that tafenoquine was reasonably well tolerated and demonstrated good protection against *P. Falciparum* for a period of up to 13 weeks after dosing. Positive parasitemia was noted in 92% of the placebo treated subjects compared to 62% in the “Tafen 25 mg” cohort; 14% in the “Tafen 50 mg” cohort; 12% in the “Tafen 100 mg” cohort; and 13% in the “Meflo 250 mg” cohort. Few adverse events were reported in the trial and there were no deaths or related serious adverse events (there were 9 SAEs all determined to be

unrelated). I defer to the review division for a full analysis of the safety and efficacy of tafenoquine in Study 043.

As described above for Study 043, the ethical acceptability of Study 045 can be assessed by evaluating the following factors; (1) Social Value; (2) Scientific Validity; (3) Fairness in subject selection; (4) Favorable risk to benefit analysis; (5) Oversight/Independent Review; (6) Respect for Persons; (7) Clinical Equipoise; and (8) Collaborative Partnership. Each of these factors are described above. Overall, in my opinion, Study 045 has high social value, is scientifically valid, demonstrated fairness in subject selection, had a favorable risk to benefit analysis, had significant oversight and independent review; demonstrated respect for persons, meet the standards for clinical equipoise at inception; and included substantial collaborative partnership.

In summary, based on my review of the information submitted by the Applicant, I believe subjects participating in Study 045 were ethically treated and their rights and welfare were adequately protected.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KEVIN A PROHASKA  
05/29/2018



NDA 210607

**REFUSAL TO FILE**

60 Degrees Pharmaceuticals, LLC  
c/o Clinical Network Services (USA) Inc.  
Attention: Fedora Daye, M.P.H.  
Senior Consultant  
8403 Colesville Road, Suite 630  
Silver Spring, MD 20910

Dear Ms. Daye:

Please refer to your New Drug Application (NDA) dated August 21, 2017, received August 21, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (b) (4) (tafenoquine) Tablets, 100 mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

**Chemistry, Manufacturing, and Controls (CMC):**

- In order to assure a suitable baseline retest date for the drug substance and expiration date for the drug product, the Agency generally expects that applicants meet the provisions of ICH Q1A (R2) and provide at least 12 months of long-term stability data for at least three primary stability batches for both the drug substance and the drug product at the time of NDA submission. The FDA may make exceptions to this minimum stability data package in the case of certain applications. Such exceptions, per the tenets of the PDUFA “commitment letter”, are agreed upon at a pre-NDA meeting. We note that the Agency recommended that you request a CMC-dedicated pre-NDA meeting (see the preliminary comments dated July 10, 2017 for your multidisciplinary pre-NDA meeting, which was subsequently cancelled at your request upon receipt of the comments). Given that you did not avail yourself of the opportunity to request this meeting or discuss this as part of your multidisciplinary pre-NDA meeting, there was no opportunity to come to an agreement regarding your final proposed stability package. Furthermore, per the PDUFA “commitment letter”, if no agreement exists between the FDA and the applicant on the contents of a complete application or delayed submission of certain components of the application, the applicant’s submission is expected to be complete at the time of original submission. The “commitment letter” further notes that incomplete applications, including applications with components that are not received within 30 calendar days after receipt of the original submission, will be subject to a Refuse-to-File decision.

While not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted.

**Biopharmaceutics:**

1. You indicate the lack of discriminating power for the proposed QC dissolution method [USP Apparatus 2 (paddle) rotating at (b) (4)



2. You acknowledged that the currently proposed QC dissolution method for (b) (4) is non-discriminating. When you resubmit the NDA, include a QC dissolution method with sufficient discriminating power for the drug product's critical quality attributes.
3. We acknowledge that Study TQ2016-02 (and TQ-2016-01) used tafenoquine tablets that have the same formulation, dosage form, manufacturing process/site/scale as the proposed commercial (b) (4) Tablets 100 mg (b) (4). If available/feasible, provide a summary table comparing the specific composition (including excipients) used (if any, in addition to the API content), and manufacturing process type (b) (4) of the 200 mg capsules that were used in key clinical efficacy trials, i.e., Studies 030, 033, 043, 045, and 058. Include in this table also the same information for the "Phase 2" and "Phase 3/final" 200 mg capsule, and the 200 mg tablet formulations evaluated in studies (e.g., Studies 014 and 022) being used to support PK bridging of clinical development formulations.

**Clinical Pharmacology:**

4. In your response dated October 11, 2017, to our October 3, 2017 Information Request regarding PK analysis datasets in electronic format, bioanalytical reports and relevant additional information in regards to the clinical pharmacology studies included in the NDA,

we acknowledge having received **Table 3** summarizing the list of pharmacokinetic and other studies and related data.

- If the NDA is resubmitted, please provide the PK datasets electronically in an analyzable ready format for the following clinical pharmacology studies to facilitate our review: **Study 022, Study 050, Study 051, Study 040, Study 015, and Study 006**.
  - In addition, we request for the location of the PK data, PK parameter estimates and other relevant requested information to be hyperlinked in **Table 3** you have provided.
5. We acknowledge that **Table 2** in **Section 2.7.2** of the NDA summarizes the Clinical Pharmacology Studies along with available bioanalytical and method validation reports in the NDA. It is however unclear why the bioanalytical reports for **Studies 006, 040, 015, and 022** and the validation report for **Study 051** were not provided.
- Please provide both, the bioanalytical reports and the method validation report for these clinical pharmacology studies, or an explanation why you are unable to provide either of these reports for the study identified. Provide the location and the hyperlink for the requested bioanalytical/method validation reports if they have already been submitted in the NDA.
6. We also acknowledge that for **Study 050**, although the individual subject plasma concentration – time data are provided in the CSR (Tables GA01 – GA15), you indicate that no PK datasets or associated documents are available, and no details of the bioanalytical method are provided in the CSR. However, we view **Study 050** to be important for our review and request that you make every effort to provide all of this information/data that is currently lacking, especially the bioanalytical method report, if you intend to resubmit the NDA, or provide an explanation why this information for **Study 050** cannot be provided.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

**PROPOSED PROPRIETARY NAME**

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at (301) 796-3414 or via email at [OSECONSULTS@cderr.fda.gov](mailto:OSECONSULTS@cderr.fda.gov)!

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely yours,

*{See appended electronic signature page}*

Sumathi Nambiar, M.D., M.P.H.  
Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUMATHI NAMBIAR  
10/20/2017