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Foreign Affairs, Defence and Trade References Committee Inquiry into the use of quinoline antimalarial drugs mefloquine and tafenoquine in the Australian Defence Force

Department of Defence

Supplementary Written Submission

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INTRODUCTION

1. The Department of Defence's written submission (the Defence submission) to the *Foreign Affairs, Defence and Trade References Committee Inquiry into the use of Quinoline antimalarial drugs Mefloquine and Tafenoquine in the Australian Defence Force* (the Inquiry) provided a comprehensive overview of Defence's efforts to protect its personnel against malaria, the antimalarial medications it has used, the antimalarial drug studies conducted in the late 1990s and early 2000s, and how Defence has responded to health concerns raised by a number of individuals in recent years.

2. Since Defence's submission was made, there have been significant developments in relation to the registration of tafenoquine. In addition, the Committee has now heard from a large number of other organisations and individuals in the course of the Inquiry, both in the form of written submissions and at public hearings. Evidence has been provided by experts in this field and those who believe they have been affected by the use of these medications. Much of the evidence submitted is complex and at times may appear contradictory.

3. This supplementary submission seeks to further inform the Committee in an effort to reduce some of this complexity and provide clarity on these issues. It provides: an update on the successful registration of tafenoquine in Australia and the US; a general overview of why and how the studies were conducted; a response to criticisms of the conduct of the studies, including the issue of informed consent; an overview of how antimalarials are used outside of the studies; more information on the side effects of antimalarials and the difficulties in diagnosing and treating those who believe they are affected; and further detail on the assistance being provided to current and former serving members.

4. It should be stated from the outset that it is not, and never has been, Defence's position to discredit individuals or de-value the experience of our members, past and present. It is also not Defence's intent to attack specific claims. Significant time has passed since the issues at the centre of this Inquiry occurred—namely, the studies conducted by the former Army Malaria Institute (AMI), now the Australian Defence Force Malaria and Infectious Disease Institute (ADFMIDI), involving the antimalarial drugs mefloquine and tafenoquine. This passage of time may affect the accuracy of the some of the evidence.

5. It is also Defence's position that the privacy of Australian Defence Force (ADF) members, both current and former, is to be respected. This is true even when Defence has evidence in personal medical records contrary to the information provided by some individuals to the Committee. Defence is committed to ensuring that all individuals are treated with respect and dignity throughout the Inquiry process, and concern for their health remains a priority.

TAFENOQUINE REGISTRATION

6. Since Defence's initial submission, tafenoquine has been registered by the United States (US) Food and Drug Administration (FDA) for use both as a single-dose for radical cure of liver-stage infections (prevention of relapse, or eradication) and for prevention of malaria in adults. This decision was applauded by infectious disease experts as "…one of the most significant advances in malaria treatment in the last 60 years"[1]. The Australian Therapeutic Goods Administration (TGA) has also recently approved tafenoquine for registration for both of these uses.

7. Details of the FDA and TGA registration outcomes and the assistance provided by Defence to these processes are provided below.

FDA Registration

8. Two separate entities have developed tafenoquine for registration in the US for two separate uses. The pharmaceutical company GlaxoSmithKline Pharmaceuticals (GSK) in association with the not-for-profit organisation Medicines for Malaria Venture (MMV) and the US Army's Walter Reed Army Institute of Research (WRAIR) has developed a formulation of tafenoquine for use as a radical cure for vivax malaria under the trade name Krintafel™. Another pharmaceutical company, 60° Pharmaceuticals (60P), also in association with the US Army, has developed a formulation of tafenoquine for prevention of malaria under the trade name Arakoda™.

9. On 12 July 2018 the FDA Anti-infective Drugs Advisory Committee voted to recommend approval of single-dose tafenoquine (Krintafel™) in patients 16 years and over for radical cure of liver-stage infections. The vote on the evidence for efficacy was unanimous (13 to zero), while the evidence for safety was 12 to one. The Committee specifically looked at the issue of neurotoxicity, and concluded that tafenoquine was "not associated with any drug-related neurobehavioral or histopathology findings…"[2]. Tafenoquine was subsequently registered for this use on 20 July 2018. A copy of the Product Information is at Annex A.

10. On 26 July 2018 the FDA Advisory Committee voted to recommend tafenoquine for the prevention of malaria in adults for up to six months. On this occasion, voting was 11 to two in favour in regards to efficacy and nine to four in favour on safety. On 8 August 2018, tafenoquine was registered by the FDA for prevention of malaria in people 18 years and older. A copy of the Product Information for this medication is at Annex B. In contrast to mefloquine, which should not be used if individuals have a history of any of a broad range of psychiatric conditions, the only situations where tafenoquine should not be used are in those individuals with a history of psychotic disorder or who have current psychotic symptoms.

TGA Registration

11. Tafenoquine has also been undergoing consideration under the regulatory processes of the TGA. At its meeting on 2 August 2018, the TGA Advisory Committee on Medicines considered that tafenoquine had a positive risk-benefit profile for the prevention of malaria in adults.

[1]Professor Ric Price, Professor of Tropical Medicine, Oxford University. Quoted in Mundasad S. New drug for recurring malaria. BBC News, 23 July 2018. Available at: https://www.bbc.com/news/health-44801139
[2] Walker M. FDA panel backs tafenoquine for 'radical cure' of malaria. Medpage Today website, available at https://www.medpagetoday.com/infectiousdisease/generalinfectiousdisease/74008

12. On 13 September 2018, the TGA approved the registration of tafenoquine, both for radical cure, under the Australian trade name Kozenis™, and for prevention, under the trade name Kodatef™. Both Kozenis™ and Kodatef™ are now on the Australian Register of Therapeutic Goods (ARTG).

ADF Assistance

13. The FDA conducted an audit of Defence's tafenoquine studies, including the tafenoquine eradication study (designated as 'Study 049') and the tafenoquine prevention study ('Study 033'), at ADFMIDI over the period 27 May to 1 June 2018[3]. The FDA auditor confirmed compliance with the approved protocols and conformity with the Declaration of Helsinki (1996) and International Conference of Harmonisation Guidelines for Good Clinical Practice (ICHGCP).

14. No major findings were recorded from the audit. Two minor findings were identified – the failure of a treating medical facility to formally notify the then AMI of a case of malaria (Study 049), and a variation in the window for final telephone follow-up (Study 033).

15. The first issue related to a failure of the treating hospital to follow Defence reporting policy at the time, which required that case details be reported to AMI to be included in the ADF Malaria Register. This did not prevent either the diagnosis of malaria or appropriate treatment being given. The member was fully aware of the diagnosis, had responded to treatment, and had subsequently submitted a claim for malaria with the Department of Veteran's Affairs (DVA) that has been accepted.

16. The second issue related to an extension beyond the protocol window for the final study telephone follow-up. The protocol required follow-up to be at the 26 week mark, but there were several instances where this did not occur for up to two months following that date. It was noted that many soldiers of this era did not have ready access to Defence computers or to mobile phones and therefore had been difficult to contact. The variance demonstrated the diligence of researchers in continuing to conduct telephone follow-up until all study participants could be contacted, even when outside the stated time limits of the protocol. It was acknowledged that this was indicative of the study team personnel doing all possible to ensure the ongoing welfare of the study participants.

17. Both issues were formally addressed with the FDA auditor at the out brief conducted on 1 June 2018, at which a representative of the TGA was also present. The audit was conducted as part of the FDA consideration for the registration of tafenoquine for both radical cure and prevention uses. It represents a thorough, independent validation of all aspects of the conduct of the studies.

18. It should be noted that Defence carefully respected the privacy of the study participants during this process and ensured that confidentiality was not breached. The audit was done in accordance with the confidentiality requirements outlined in the information sheet and consent forms for the studies.[4]

19. The pivotal contribution of the ADF to the registration of tafenoquine has been recognised by those involved in this process. Defence has been advised that the use of the syllable 'koda' in the trade names Arakoda™ and Kodatef™ reflects the famous Kokoda Trail campaign of World War Two in recognition of this contribution. Defence would like to thank all of the participants, study team, and others involved in these studies for their individual contributions to making sure that the generations to follow have access to this life protecting and saving antimalarial medication.

[3] The tafenoquine treatment study was designated as 'Study 046'
[4] The information sheets/consent forms are at Annexes G and H of Defence's submission to the Senate Inquiry

THE ANTIMALARIAL STUDIES

20. As previously stated, the matters under inquiry by the Senate Committee are complex, particularly given the events in question occurred over 16 years ago. A number of matters have been raised in relation to the studies, particularly in the public hearings, that indicate a degree of confusion as to why and how the studies were conducted. While some of these matters were dealt with in the initial Defence submission, more information and clarification is provided below.

Reasons for the Studies

21. Some individuals who have made submissions to this Inquiry have shared their opinion that the ADF did not have a valid reason to conduct these antimalarial studies using ADF members. This is strongly disputed by Defence.

22. Malaria is no longer present in Australia and therefore ADF members have no natural immunity to the disease. Experience has shown that malaria is not just a theoretical risk to the ADF, with the disease having actually stopped combat operations in 1918, 1943 and 1968. This is why it is imperative that ADF personnel are adequately protected when they deploy to malarious areas.

23. Medications need to be studied in the population in which they will be used. Importantly, ADF members are exposed to a far higher risk of malaria when deployed than recreational travellers to the same countries as they largely operate outside urban environments. It is crucial to understand how malaria prevention strategies, including antimalarial medications, work under real life field conditions. Such understanding enables appropriate force protection countermeasures to be developed and implemented.

24. The Defence submission attempted to describe why particular antimalarial studies were undertaken by the ADF. The driving reason was to protect ADF personnel from the threat of a deadly disease in a region where malaria was endemic and antimalarial drug resistance was problematic. Defence was acutely aware that there were only two effective preventive antimalarials on the ARTG at the time of the studies, and that in the initial stages of Australia's involvement in the International Force East Timor (INTERFET), soldiers who were taking the first-line medication, doxycycline, were being diagnosed with malaria.

25. The first case of malaria diagnosed in an Australian Army soldier in Timor-Leste was in the first month of deployment in 1999, and a further 63 cases were recorded during INTERFET[5]. A further 212 developed malaria after returning to Australia following the standard eradication regimen of doxycycline and primaquine. While this was thought to be a compliance problem (doxycycline needs to be taken daily, which is difficult in a deployed setting, and missed doses can result in a loss of protection), the possibility existed of the development of resistance to doxycycline. The use of an alternative medication was therefore considered.

26. At that time tafenoquine, a new medication that had already been tested in over a thousand people, was already being studied in Bougainville for eradication of malaria and compared with primaquine, which was the standard eradication medication. This study, referred to throughout this submission as the tafenoquine eradication study, was being done because there had been cases of relapsing malaria in recent deployments, and, again, it was not known whether it was a compliance problem with primaquine (a 14 day course) or the malaria parasite developing resistance to it. Tafenoquine, given as a three day course, was already showing great promise as an antimalarial, both in terms of its efficacy (i.e. protection against malaria) and its safety profile. These studies were then continued in Timor-Leste.

[5] Kitchener S, Auliff A, Rieckmann K. Malaria in the Australian Defence Force during and after participation in the International Force in East Timor (INTERFET). *Med J Aust*. 2000 Dec 4-18;173(11-12):583-5

27. Due to the favourable experience with tafenoquine, it was then considered for study in the ADF as a preventive medication. The main benefit it offered over doxycycline was that it was taken once a week, thus compliance was easier and missing a dose on a particular day was unlikely to alter its effectiveness. The opportunity was presented to test it in a randomised, controlled, 'double-blind' study. This means that neither soldiers or researchers knew which medication was being taken until it was 'unblinded' at the end of the study or when a participant developed side effects. The value of a double-blind study is that it eliminates any bias in outcomes. Often these types of studies use a placebo as a comparator but this was not ethical in this situation as soldiers needed to be protected against malaria. Thus mefloquine, the only weekly antimalarial registered for prevention of malaria, was used as the comparator. This study is referred to throughout this submission as the tafenoquine prevention study.

28. The study was a success with no diagnoses of malaria occurring for either group during deployment, which was quite different from the early experience when using doxycycline. The tafenoquine prevention study was only ever intended to be of limited duration – the six month deployment of a battalion group to Timor-Leste. However, given the issues with doxycycline, it was considered prudent to reconsider whether a weekly antimalarial should continue to be preferentially used. Tafenoquine was still under development and was not yet registered, therefore could not be considered, but this was not the case for mefloquine.

29. At this time mefloquine was known to be effective against malaria, had been registered in Australia for over ten years, was recommended for use in NHMRC guidelines, was commonly used by civilian travellers, could be taken once a week, and was the antimalarial of choice for other militaries. Nevertheless, instead of changing the policy immediately, a decision was made to adopt the more cautious approach of undertaking a post-marketing clinical study comparing mefloquine to doxycycline under field conditions.[6] The advantage of this approach was that Defence was able to control, closely monitor and document the use of mefloquine and compare it with doxycycline, both in terms of efficacy and tolerability (side effects). This field study, referred to as the mefloquine versus doxycycline study, was conducted during the next two battalion rotations into Timor-Leste: 4RAR and 2RAR.

30. Only one case of malaria occurred in Timor-Leste during this study in a soldier who had started on mefloquine but had been switched to doxycycline and had been unable to take it on a daily basis. Overall, the study found that mefloquine was generally well tolerated but that there was no real difference between the efficacy of the two medications if attention was paid to compliance. Doxycycline, being an antibiotic, also had the advantage of providing some protection against other insect borne diseases, such as typhus and leptospirosis. On this basis, Defence saw no compelling reason to change its policy.

[6] As mentioned in the Defence submission, the need for such a study had been identified in a recent Cochrane Review - Croft AM, Garner P. Mefloquine for preventing malaria in non-immune adult travellers. *Cochrane Database Syst Rev.* 2000;(4):CD000138

Mefloquine and tafenoquine use

31. The Committee has requested further clarification regarding who was provided mefloquine or tafenoquine during Timor-Leste deployments[7], including how many soldiers from the 131 Locating Battery, Royal Australian Artillery received mefloquine when they deployed to Timor-Leste in 2000[8]. The Committee has also requested clarification as to whether all those deploying to Timor-Leste were given mefloquine, and who was given tafenoquine[9].

32. Table 1 provides an overview of how many individuals took these medications in the various studies, what unit or Battalion Group the participants came from, and the approximate dates of the studies. It does not include every single unit that made up the deploying Battalion Group. The eradication and treatment studies included personnel from a large number of units in addition to those listed.

Study	Medication	No. of participants	Location	Dates	Unit (or Battalion Group)
Tafenoquine for eradication[10]	Tafenoquine Primaquine	1017 (378/639) 464	Bougainville/ Timor-Leste	February 1999 to April 2000	3 RAR, 5/7 RAR, others
Tafenoquine prevention[11]	Tafenoquine Mefloquine	492 162	Timor-Leste	October 2000 to April 2001	1 RAR
Mefloquine vs doxycycline prevention[12]	Mefloquine Doxycycline	1157 388	Timor-Leste	Apr - Oct 2001; Oct 2001 to Apr 2002	4 RAR; 2 RAR
Tafenoquine for the treatment of malaria[13]	Tafenoquine	31	Australia	Between 2000 and 2001	Various

Table 1: ADF antimalarial studies 1999 to 2002

[7] Senate Foreign Affairs, Defence and Trade References Committee. Use of the Quinoline antimalarial drugs Mefloquine and Tafenoquine in the ADF - 30/31 August - Q4 - Mefloquine and Tafenoquine figures
[8] Senate Foreign Affairs, Defence and Trade References Committee. Use of the Quinoline antimalarial drugs Mefloquine and Tafenoquine in the ADF - 30/31 August - Q1 - 131 Locating Battery
[9] Senate Foreign Affairs, Defence and Trade References Committee. Use of the Quinoline antimalarial drugs Mefloquine and Tafenoquine in the ADF - 30/31 August - Q5 - Timor
[10] Elmes N, Nasveld P, Kitchener S, et al. The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of *Plasmodium vivax* malaria in the Southwest Pacific. *Trans R Soc Trop Med Hyg.* 2008 Nov;102(11):1095-101.
[11] Nasveld P, Edstein M, Reid M, et al. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. *Antimicrob Agents Chemother*. 2010 Feb;54(2):792-8.
[12] Kitchener S, Nasveld P, Gregory R, et al. Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor. *Med J Aust* 2005; 182 (4): 168-171.
[13] Kitchener S, Nasveld P, Edstein M. Tafenoquine for the treatment of recurrent *Plasmodium vivax* malaria. *Am J Trop Med Hyg*. 2007 Mar;76(3):494-6.

33. No individual was given tafenoquine outside of these studies; however, a number of individuals were prescribed mefloquine, either because they could not tolerate the first-line medication, doxycycline, or, in the case of some personnel who deployed with the 1RAR Battalion Group but who were not participants in the studies, to simplify health surveillance activities by aligning dosage requirements with the rest of the group. In these latter circumstances it was an individual choice as to whether they wished to take doxycycline or mefloquine. The exact number of individuals who were prescribed mefloquine during Timor-Leste deployments outside of the studies is unknown as Defence did not have a complete electronic dispensing record until 2001 (more information is provided on this in paragraph 98).

34. It is understood the 131 Locating Battery, Royal Australian Artillery, deployed with the 1st Royal Australian Regiment (1RAR) Battalion Group to Timor-Leste in 2000. The tafenoquine prevention study drew participants from the 1RAR battalion group but the study nominal roll does not include any members of the 131 Locating Battery. As this unit was based in Enoggera near Brisbane, it is likely that these individuals did not arrive in Townsville until after the study recruitment period. In 2001, 18 members of 131 Locating Battery, Royal Australian Artillery, deployed with the 4 RAR Battalion Group to Timor-Leste and participated in the mefloquine versus doxycycline comparison study. Of these, 16 members took mefloquine and two took doxycycline.

The '100 Club'

35. The Committee has heard several individuals refer to being in the '100 Club' and has requested more information on these matters[14]. Approximately 100 individuals were selected at the beginning of the tafenoquine prevention study for additional testing and assessment pre-, during and post-deployment[15]. The designation of 'the 100 Club' was not given by researchers but was a self-assigned colloquial term or nickname for this sub-group. For scheduling reasons the sub-group was predominantly from 1RAR Bravo Company.

36. The extra follow up included eye and lung function tests that were done before (within three weeks) and after (within four weeks) deployment, and the taking of an additional 20mls of blood over and above that taken for every other study participant.

37. Eye function testing involved an ophthalmologist conducting a 'slit lamp' examination. This involves examining the eye through a device that stabilises the head and provides magnification and illumination to view the surface of the eye, eyelids, cornea, retina and associated structures. The volunteers also had standardised assessments of vision and colour perception.

38. Lung function testing included assessing the diffusion capacity of the lungs to carbon monoxide (DLCO). This involves a non-invasive 'single-breath' technique where the volunteer exhales through plastic tubing and then breathes in a breath of a gas mixture (carbon monoxide and an inert tracer gas), holding their breath then exhaling as a sample of the expired gases is analysed by the DLCO machine. This took approximately five minutes and was repeated three times. The volunteers also had a chest X-ray and a standard lung test (spirometry) to exclude pre-existing abnormalities.

39. The additional 20ml blood sample was used to measure methaemoglobin levels in the blood. Methaemoglobin is a variation in the oxygen carrying haemoglobin protein in the blood. Increased levels can impair the blood's oxygen carrying capacity and certain drugs are known to increase blood methaemoglobin.

[14] Senate Foreign Affairs, Defence and Trade References Committee. Use of the Quinoline antimalarial drugs Mefloquine and Tafenoquine in the ADF - 30/31 August - Q6 - '100 club'

[15] This information formed part of the information sheet/consent form which was provided at Annex G of Defence's submission to the Senate Inquiry

40. If a significant anomaly was identified in tests the participants were appropriately investigated and followed up until resolution, as was the case for all participants. An important finding in this subgroup were the changes on the surface of the eye (cornea) called vortex keratopathy found in a number of those who had taken tafenoquine. These changes did not affect vision and would probably not have been found if the additional eye examination had not occurred. This reflects the high level of care afforded to the participants of the studies. All of these volunteers were subsequently followed up by an ophthalmologist until the changes had fully resolved and all resolved within six months of return to Australia.

41. This sub-group were given the same antimalarials (either mefloquine or tafenoquine) as all other study participants and, apart from the additional testing, were managed, monitored and followed up in exactly the same way. This included specific follow-up for up to 12 months and the provision of a study card that advised them and their medical practitioner of what to do and who to contact if they were to develop fever in the six months after the study**.** As well as the specific follow-up conducted as part of the studies, standard post-deployment assessments were provided for all personnel who participated in these studies, including a return to Australia medical and psychological screen (RtAPS). Three months after return, they also had a comprehensive medical assessment and a post-operational psychology screen (POPS).

42. While serving all participants continued to be monitored through Annual Health Assessments (AHA), which were standard practice for the ADF until 2011 when the new evidence-based Periodic Health Examination schedule was implemented. The AHA involved the member being asked a comprehensive set of questions regarding symptoms across all areas of the body. If any symptoms were reported, the individuals were referred for medical officer review and managed accordingly.

Information provided to study participants

43. The Committee has heard from several individuals that they were not provided sufficient information or were lied to regarding the drugs they were being given and their side effects, including that they were not told that tafenoquine was not yet a registered medication. The implication is that they were therefore unable to provide informed consent. Defence strongly refutes this allegation.

44. All participants were verbally advised that tafenoquine was a drug under development. For the tafenoquine prevention study, the combined information sheet and consent form indicates that tafenoquine is a "new drug" that "has not been registered in Australia" and is "still defined as an 'experimental' compound"[16]. Participants of this study were also advised that the study was double-blinded and that they would not know which drug they were on while the studies were being conducted.

45. Participants were not misled regarding side effects; they were briefed in accordance with information known at that time. The briefings included discussion of known potential adverse events and, in relation to mefloquine, included information on the reports of psychiatric events. This was based on the information known at that time, which indicated that such events occurred in 1 in 10000 individuals. It was also reinforced that those with a history of psychiatric conditions, anxiety, depression and epilepsy should not volunteer for the study.

[16] See Annex G of Defence's submission to the Senate Inquiry

46. In regard to tafenoquine, the known potential adverse events at that time were related to drug intolerance (symptoms such as vomiting, nausea and diarrhoea) and were drawn from the preceding tafenoquine clinical studies. No specific mention of neuropsychiatric adverse effects or past history was made in relation to tafenoquine as these had not been reported, however for the prevention study these elements were emphasised because the study was double-blinded and participants could be receiving mefloquine. These discussions were reflected in the consent forms for the studies.

Deployment of those not participating in the studies

47. During the public hearings the Committee has engaged in discussion regarding the numbers of individuals who did not participate in the studies but still deployed, particularly in the context of the tafenoquine prevention study.

48. The Inspector General ADF (IGADF) Inquiry into the conduct of the studies and the testimony of Lieutenant General Caligari[17] both indicated that over 400 individuals on the 1 RAR Battalion Group deployment did not participate in the study. This demonstrates that it was not mandatory to be on the study in order to deploy. No evidence has been presented that anyone was stopped from deploying because they refused to participate in the studies.

49. The overall number of personnel who declined to participate across all studies is difficult to ascertain as there was no requirement in the study protocols to record reasons why members were not specifically recruited. This was in part intended to ensure that members did not have to disclose to their colleagues the reasons why they may not be study participants. In addition to not consenting, study exclusion criteria included blood test results, past medical conditions, and availability in location to undertake the loading dose under observation.

50. For the tafenoquine prevention study, 95 personnel were recorded as being unwilling or unable to enrol and another 24 were excluded as they were found unsuitable on screening. Of these, 40 were Privates or Lance Corporals, 27 were Corporals, 27 were Senior Non Commissioned officers, and 25 were officers up to the rank of Major.

51. Those deploying who were not on the studies were still required to take an antimalarial, and this was either doxycycline or mefloquine (see paragraph 33 for more information on this).

The use of a loading dose

52. The Committee has requested additional information on the use of a loading dose for those taking mefloquine or tafenoquine (for prevention) as part of the studies[18]. Taking a three day loading dose at the start of a course of mefloquine when used for prevention is standard Defence practice. A three day loading dose was also used for those taking tafenoquine during the studies.

[17] Senate Foreign Affairs, Defence and Trade References Committee. Use of the quinolone antimalarial drugs mefloquine and tafenoquine in the Australian Defence Force. Townsville Public Hearing, 31 August 2018, p 22

[18] Senate Foreign Affairs, Defence and Trade References Committee. Use of the Quinoline antimalarial drugs Mefloquine and Tafenoquine in the ADF - 30/31 August - Q7 - 'loading doses'

53. Mefloquine and tafenoquine both have a long half-life and therefore it can take several weeks for sustained protective levels of the drug to be reached. This is a problem when preparing forces for deployment at short notice as it could mean that soldiers are unprotected for periods during the initial deployment period. A loading dose prior to deployment achieves protective levels more quickly. Mefloquine loading doses of 250mg daily for three consecutive days have been shown to result in steady state blood concentrations in three days as compared with seven to 10 weeks when weekly dosing is used[19]. Taking a loading dose before deployment also allows any side effects to be identified before deployment and for the medication to be stopped if necessary

54. A loading dose prior to travel or deployment has long been recommended in the literature. While not specifically mentioned for this purpose in the Lariam™ Product Information for Australia[20], it is recommended in that of other countries such as New Zealand[21]. A loading dose of tafenoquine when used for prevention of malaria is recommended in the newly published Product Information.

55. The importance of a loading dose of mefloquine in an operational setting had been well demonstrated in other militaries by the early 2000s. A deployment of US Marines to Somalia in 1993 experienced high rates of malaria in those who changed from doxycycline to mefloquine without loading doses[22]. The paper detailing this experience concluded that military personnel and other travellers to highly malarious areas who are taking mefloquine for prevention should either take several weekly pre-travel doses or employ a loading dose. The loading dose regimen was subsequently trialled in US Marines in a non-endemic area and found to be effective and tolerable[23].

56. In May 2000, the UK forces rapidly deployed two battalions to Sierra Leone, and could not achieve sufficient pre-exposure dosing due to time and supply difficulties. At that time, the UK did not advocate a loading regimen. A large number of falciparum malaria cases resulted[24].

57. The failure to provide Australian soldiers deploying into Timor-Leste with a loading dose of mefloquine would have ignored the real-life experience gained by both the USA and UK forces and placed ADF members at unnecessary risk of malaria. Defence therefore ensured that all those who received mefloquine were given a loading dose before deployment. This remains standard practice.

Medical Officer role in the tafenoquine eradication study

58. Some individuals have claimed that they did not see a doctor before participating in the tafenoquine eradication studies. It was a study requirement for all individuals to be briefed and consented by a doctor. If this didn't occur then the individual was not considered for the study. It is possible that the medications themselves were handed out by other health staff as this was common practice on deployments (see paragraphs 103 to 106).

[19] Roche. Product and Consumer Medicine Information Licence, Lariam ®, Mefloquine Hydrochloride (Australia).
[20] The Lariam™ Product Information in Australia does recommend a loading dose for treatment with mefloquine. Roche. Product and Consumer Medicine Information Licence, Lariam ®, Mefloquine Hydrochloride (Australia) (see Annex B to Defence's submission).
[21] See New Zealand PI for Lariam™ on the New Zealand Medicines and Medical Devices Safety Authority website: http://www.medsafe.govt.nz/profs/datasheet/l/lariamtab.pdf
[22] Wallace MR, Sharp TW, Smoak B, Iriye C, et al Malaria Among United States Troops in Somalia. Am J Med 1996: 100: 49-55
[23] Boudreau E, Schuster B, Sanchez J, et al. Tolerability of prophylactic Lariam regimens. Trop Med Parasitol 1993; 44: 257-265
[24] Tuck J, Andrew Green A, Roberts K. Falciparum malaria: an outbreak in a military population on an operational deployment. Military Medicine 168: 8: 639-642

Reporting of side effects

59. The Committee heard testimony from several individuals that they had reported side effects during the studies but were ignored, and/or that they were told to remain on their medication regardless.

60. Side effects could be reported by members in two ways – either to the study team doctors through the structured interviews conducted at programmed intervals during the study, or by reporting to their supporting health element. If reported by the former, individuals were referred to the supporting health element for review. The health provider would then consider the start and finish dates of symptoms, the relationship to times of dosing, and whether the member and/or health provider believed that the symptoms were related to the drug or another cause. Examples of the latter could be vertigo associated with motion sickness from travelling in the back of a closed Armoured Personnel Carrier, or sleeping problems due to the proximity of aircraft operations. If symptoms were severe and thought to be associated with the antimalarial medication being taken, or if requested by the individual, the medication was ceased and an alternative provided.

61. All adverse events reported by study participants were recorded contemporaneously by two methods. The first was in the study Case Record Form, which was used to collect data for the study. The second was by a form known as the 'PM105', which was where all health treatment data on individuals was recorded at that time. These were later filed in individuals' medical documents.

Recording of Study Information

62. It was implied by several individuals that study documentation had been removed from their medical record.

63. The study Case Record Form documents, where study related data was recorded, did not form part of the normal health record and were never included in the medical records. However, as indicated above, clinically relevant information was generated from the studies including test results and PM105s. These were subsequently placed on both the Unit Medical Record (UMR) and later Central Medical Records (CMR) of participants in accordance with Defence practice at the time. Transfer of clinical information recorded on deployment occurred via this process irrespective of whether a member was a study participant or not. It is acknowledged that, as the health records were paper based at this time, the potential existed for pages to be lost and not filed in the UMR or CMR. It is likely that this occurred in some cases.

64. Where participants were seen through routine health support elements such as the Unit Regimental Aid Post (RAP), the documentation was added to the member's UMR and CMR and copies of notes were also made available to AMI.

65. Since 2016, when a serving member has requested and been provided with their study documentation, this additional information has been added to the Defence electronic Health System (DeHS).

Availability of Study Protocols

66. There was some confusion at the Brisbane public hearing regarding the availability of the tafenoquine prevention study (referred to as 'Study 033') protocol[25]. This protocol is not commercial-in-confidence as was indicated in evidence but was marked 'in-confidence' at the time it was submitted to the relevant Ethics Committee. The original and amended protocols for this study, as well as a plethora of related documentation, were released on 10 January 2017 under the *Freedom of Information Act 1982*[26]. These documents are attached to this submission (Annex C).

67. It should be noted that the protocol was modified over time, and that each modification was subsequently provided to the Ethics Committee for clearance as is standard practice. Modifications to protocols are not unusual in the evolution of clinical studies.

68. Study protocols for other studies are available upon request.

Notification letters following the tafenoquine prevention study

69. The Committee heard that a number of individuals received contradictory letters following the tafenoquine prevention study. This has been confirmed and was due to a clerical error. In accordance with the study protocols, researchers wrote to all participants once the data was 'unblinded' (i.e. it became apparent which medication people were on) advising them which of the medications they had been taking. Unfortunately, all participants originally received a letter stating that they had been taking mefloquine. This was corrected with subsequent correspondence where appropriate. Additional letters were provided to participants who had taken tafenoquine to advise then of the finding of vortex keratopathy in some participants who had taken tafenoquine, and that the condition was benign and resolved completely after tafenoquine was stopped.

[25] Senate Foreign Affairs, Defence and Trade References Committee. Use of the quinolone antimalarial drugs mefloquine and tafenoquine in the Australian Defence Force. Brisbane Public Hearing, 30 August 2018, p 23
[26] FOI 180/15/16

ETHICAL CONDUCT OF STUDIES AND INFORMED CONSENT

70. Several written and verbal submissions, including those of the Quinoline Veterans and Families Association[27] and the Quinism Foundation[28], have implied that there was scientific and/or criminal misconduct by the researchers involved in the antimalarial studies. Many former serving members have claimed that they were used as 'guinea pigs' in the studies. There have also been allegations that the motivation for undertaking the tafenoquine studies was a financial one and that there has been collusion with pharmaceutical companies. The question of whether it is possible to give informed consent in a military context at all has also been raised.

71. As detailed in Defence's submission, the study research methodology was sound, consistent with international guidelines, and ethical, having been scrutinised, cleared and later audited by the extant Defence Human Research Ethics Committee. This includes the requirements put in place to ensure informed consent. The papers produced from these studies were extensively peer reviewed and published in leading scientific journals. The studies have also been independently reviewed by an IGADF Inquiry (see paragraphs 84 to 88 for more detail) and, more recently, an FDA audit (see paragraphs 13 to 17). These activities represent independent assurance of the validity and ethical good standing of the studies. Defence therefore denies any allegations that the studies were conducted in an inappropriate or unethical manner.

72. Some of the issues around the conduct of the studies are addressed in more detail below.

Informed Consent

73. The Committee has heard opinions that informed consent is incompatible with military service due to the hierarchical nature of the military. It has therefore been implied that undertaking clinical studies on military personnel is inappropriate in all circumstances.

74. The ADF strongly supports an individual's right to either participate in research or decline to do so. While ADF members are required to follow lawful orders, their participation in research and in their own health care cannot be forced. Their best interests are taken into account by researchers and protected by an independent Ethics Committee.

75. The current Departments of Defence and Veterans' Affairs Human Research Ethics Committee (DDVA HREC), like its predecessors, is a properly constituted and registered ethics committee. Its membership includes a lawyer, lay people, a pastoral care member, a civilian clinical care provider and others with experience in the types of research being considered by the Committee. The DDVA HREC also includes a Defence health graduate and a contemporary veteran. The members are personally appointed to each category of membership and are not representatives of Defence or DVA. A significant number of the members are from outside of Defence.

76. As detailed in the Defence submission, the National Statement on Ethical Conduct in Human Research recognises military personnel as a potentially vulnerable population with respect to volunteering and consenting to participation in research[29]. The DDVA HREC is acutely aware of this and is very stringent in its review of research proposals to ensure that there is no coercion, real or perceived, in the recruitment of participants from the ADF. For example, research in new military recruits, who may perceive that their participation is expected, is rarely approved.

[27] Submission 16 to the Senate Inquiry - The Australian Quinoline Veterans and Families Association
[28] Submission 17 to the Senate Inquiry - The Quinism Foundation
[29] National Health and Medical Research Council. *National Statement on Ethical Conduct in Human Research (2007) (Updated 2018). Chapter 4.3: People in dependent or unequal relationships*. Available at: https://www.nhmrc.gov.au/_files_nhmrc/file/publications/national-statement-2018.pdf

77. The DDVA HREC also ensures that the information provided to prospective participants emphasises that participation is voluntary, that there is always an option to withdraw from participation at any time, and that there will be no detriment to the individual should they choose not to participate or to withdraw. Minutes of the Ethics Committee meetings relating to the ADF antimalarial studies released under the *Freedom of Information Act 1982* demonstrate the Committee's requirements for amendments to the submitted information sheet and consent form to ensure these provisions were included.

78. Recruitment through the chain of command is not permitted and prospective participants must be given adequate time and opportunity to ask questions and consider their participation. The DDVA HREC monitors all approved research to ensure the research is being conducted in accordance with the approved provisions.

79. It is a similar situation in the provision of health care and force health preparation more generally. Prior to entry into the ADF, applicants are advised of medical requirements, such as blood tests and vaccinations, so that they are appropriately informed and can decide whether or not they want to proceed. If they choose not to undergo these requirements, they have the option of withdrawing their application.

80. In service, ADF members may decline a particular health intervention. Those who decline vaccination or any other treatment that is deemed necessary for them to safely deploy or work will not be forced to undertake this treatment; however, there may be consequent implications for their employment or deployment. For example, a member may not be permitted to deploy on operations if they have not been fully prepared from the health perspective. This is a duty of care and safety issue: it would not be appropriate to allow members to deploy if they are not adequately protected against known and preventable infectious disease risks.

81. If a member declines a particular treatment then their medical employment classification may be reviewed and employment restrictions applied to ensure they are not put at undue risk in the military environment. At all stages, the members are informed of what is required, why and of the risks that might be associated with their decision. It is acknowledged that some ADF members may just comply with medical requirements because they believe that is what is expected. However, if a member genuinely does not want to undergo a particular intervention, they are afforded their basic rights and not forced to do so. They are counselled about the risks, benefits and potential consequences, and are given the opportunity to make an informed decision.

82. It is important to note that the routine vaccinations and other preventative medications provided in the ADF are usually mainstream countermeasures approved for use in Australia and used widely in the civilian community. Clinical treatment is provided in accordance with best practice clinical guidelines. Any medicine or treatment that is still deemed experimental or is not approved for routine use in Australia is managed through a formal informed consent process. For example, a cancer patient whose specialist offers them a place in a clinical treatment trial will be counselled to ensure that they make their own decision once they fully understand the risks and benefits. Highly specialised vaccines or medicines that may need to be used as countermeasures against particular threats, such as nuclear, biochemical or exotic infectious diseases threats (such as Ebola), are only administered after the provision of fully informed written consent.

83. Any potential constraints that might be put on clinical research due to concerns about informed consent must be balanced against the considerable direct benefits that have been obtained by participants in clinical studies of novel drugs to treat a variety of medical conditions. While some research may not infer direct benefit to the individual, everyone has the right to choose whether or not to participate for their own future benefit, or the benefit of others.

The Inspector General ADF (IGADF) Inquiry

84. Several submissions to the Inquiry have expressed dissatisfaction with the conduct, outcomes and neutrality of the IGADF Inquiry conducted in 2016[30]. More clarification on the nature of the Inquiry and its independence is provided below.

85. The Inquiry was conducted by Brigadier Andrew Dunn CSC, at the direction of the then-IGADF (Mr Geoff Earley) following a complaint from Major Stuart McCarthy. Brigadier Dunn is a highly experienced and qualified legal officer with over 35 years' experience in the ADF. He served in the permanent Army (ARA) from 1982-2011, deployed on operations on five occasions, including a six-month deployment to Timor-Leste in 2000, and now serves in the Army Reserves. He has held many appointments in the ADF, including the Director of Army Legal Services and the Director of Military Justice (Administrative and Discipline Law), and is a former Deputy Inspector-General of the Australian Defence Force. Brigadier Dunn has conducted, assisted, or reviewed many administrative inquiries including Boards of Inquiry.

86. An important contextual point is that the IGADF antimalarial drug study inquiry examined whether the 2000 to 2002 antimalarial drug studies were conducted ethically and in accordance with national guidelines. The principal focus of the Inquiry was to determine whether relevant processes and national guidelines existing at the time for the conduct of clinical studies had been observed, including an examination of the issues of voluntary participation and informed consent. The Inquiry did not examine the general use of mefloquine or tafenoquine by Defence members, or the side effects that may be caused by those antimalarial drugs, as these were medical issues which fell outside IGADF's military justice jurisdiction. Therefore, expert medical opinion on this issue was not required.

87. The Inquiry also examined whether Major McCarthy had been threatened with disciplinary action for expressing concern about individuals allegedly affected by mefloquine. Finally, the Inquiry examined whether a named Defence health officer had become aware of neurotoxic adverse side effects of mefloquine and had failed to disclose this to senior Defence officials.

88. The Inquiry procedure for gathering relevant evidence included obtaining information from witnesses, including witnesses identified by Major McCarthy and also expert witnesses. The Inquiry procedure also included an extensive review of the study documentation, and the collection of supporting and reference documents. These documents included national guidelines, protocols, policy and procedures relating to the conduct of research studies, and the Human Research Ethics Committee approvals relating to the studies. The IGADF Inquiry found that the studies had been conducted ethically, according to relevant regulations and that no violation of military law had occurred.

Claims that soldiers were used as 'guinea pigs'

89. The highly emotive and misleading term 'guinea pig' is variously defined as anything from "a subject of research, experimentation, or testing"[31] to a description of someone where "…something is tested on them that has not been tested on people before" [32]. While the first definition obviously applies to the participants in these or any other studies, the second definition does not apply.

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[30] Inspector General ADF. *Inquiry Report into issues concerning antimalarial trials of the drug mefloquine between 2000 and 2002 involving Australian Defence members deploying to East Timor*. 2016, paragraphs 158, 170, 233. Available at http://www.defence.gov.au/Publications/COI/Docs/COI-AntiMalarialTrials.pdf

[31] Merriam-Webster Dictionary (online)

[32] Collins English Dictionary (online)

90. At the time of the studies, mefloquine was already registered and had been used widely in both military and civilian populations. While tafenoquine had not been registered, it had previously been used in large numbers of people in clinical studies. In addition, participants provided informed consent, participation was voluntary, and the drugs were administered in accordance with Ethics Committee approved study protocols and/or through permission from the TGA.

91. All study participants were monitored much more intensely and carefully than was usual for deployed ADF personnel who were given antimalarials to protect against malaria in accordance with extant policy. As the Committee heard in Brisbane, in the case of mefloquine this was perhaps an overly cautious but entirely appropriate approach given that Defence had limited experience with this medication at that time[33].

Alleged collusion with pharmaceutical companies

92. It has been alleged that the pharmaceutical companies involved in the development of tafenoquine, and perhaps also ADF officials, stand to make millions of dollars from the registration of tafenoquine. This is strongly denied. No ADF official has a financial interest in tafenoquine or any other antimalarial. In addition, as noted in the Defence submission, antimalarial medications are not regarded as very profitable and rely on entities such as the US Army and not-for-profit organisations such as the Medicines for Malaria Venture (MMV) to advocate for their registration.

93. Although it is not possible to be certain of the total investment required for the development of tafenoquine, it is likely to be in excess of US$1 billion. It is understood that GSK has spent in excess of $100m on the recent FDA registration process alone. Some of these costs will be recouped under a system known as a Priority Review Voucher. This is a means by which the US Government subsidises drugs that do not have viable commercial markets but are needed for important niche markets (these are known as ‘orphan drugs’). As the first company to obtain registration for tafenoquine, GSK received a voucher under this system thought to be valued at an estimated US$100m.

94. It is estimated that the global roll out of tafenoquine, which has yet to occur, will in fact cost more than US$100m and it is likely that it will require continued subsidy, as is the case for many of the current antimalarial drugs, because it will largely be used in developing countries. The US military also continues to invest a great deal of money in tafenoquine because it is required for force health protection.

[33] Senate Foreign Affairs, Defence and Trade References Committee. Use of the quinolone antimalarial drugs mefloquine and tafenoquine in the Australian Defence Force. Brisbane Public Hearing, 30 August 2018 p 24

GENERAL USE OF ANTIMALARIALS BY DEFENCE

95. Several questions have arisen in the course of the Inquiry as to how Defence has used, and continues to use, preventive antimalarial medications for ADF members on deployments outside of the specific studies detailed in Table 1, including how many individuals have been prescribed mefloquine in these situations. It is reiterated that no individuals have been given tafenoquine outside of the studies.

Prescription of mefloquine outside of the studies

96. Since January 2001, 666 personnel have been prescribed mefloquine outside of the ADF Malaria and Infectious Disease studies. Table 2 provides a year by year break down of these prescriptions. The figures in the early years of this table include those deploying to Timor-Leste who were given mefloquine outside of the antimalarial studies.

2001	2002	2003	2004	2005	2006	2007	2008	2009
94	77	69	67	73	53	28	32	29
2010	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**[34]
25	26	13	20	35	15	5	2	3

Table 2: Number of ADF members who were prescribed outside of the antimalarial studies from 01 January 2001

97. From the early 1990s to 2006, mefloquine was used by Defence as its second line preventive antimalarial; that is in circumstances where individuals were unable to tolerate doxycycline or for whom it was unsuitable. Intolerance to doxycycline is a common event and a second line antimalarial prevention drug is required particularly for those with severe gastrointestinal symptoms or photosensitivity (intolerance to sunlight), which can be especially problematic in tropical environments. As it was mandatory to be on a preventive antimalarial for force protection reasons, mefloquine was at that time the only choice for those deploying who could not tolerate doxycycline[35]. Therefore, as the Committee has heard, a small number of individuals in earlier deployments were prescribed mefloquine.

98. As described in paragraph 33, the exact number of individuals who were prescribed mefloquine outside of the studies prior to January 2001 is not known as Defence did not have a complete electronic dispensing record until this date. The only way to establish this number would be to review the hard copy medical documents of ADF members who deployed into malarious areas before this time.

Choice of antimalarials

99. The Committee has specifically questioned why some members involved in the studies were given doxycycline rather than mefloquine on subsequent deployments[36]. This is because, notwithstanding the fact that the studies were successful and that most users tolerated mefloquine or even preferred it (94 per cent of soldiers taking mefloquine at the end of their deployments indicated they would use it again), doxycycline remained the preferred (first-line) medication for prevention of malaria. Tafenoquine was not an option as it was not registered at the time.

[34] To 31 August 2018
[35] This changed in 2006 when atovaquone/proguanil was officially adopted in policy as the second line antimalarial.
[36] Ibid, p 22

100. The Committee has also heard opinions from individuals that atovaquone/proguanil, more commonly known by its trade name Malarone™, could have been used as an alternative to doxycycline rather than conducting the mefloquine and tafenoquine studies. It has also been implied that the then AMI staff recommended against the adoption of Malarone™ due to cost[37].

101. Atovaquone/proguanil was tested for use in prevention of malaria in ADF personnel in Bougainville during the late 1990s[38], however it was not registered for use in Australia for prevention until late 2001, by which time the Timor-Leste studies were well underway. In addition, atovaquone/proguanil, like doxycycline, requires a daily dose, and therefore has similar compliance issues.

102. In terms of the financial aspects, the quoted paper did comment on the significantly increased cost of atovaquone/proguanil compared with doxycycline as a factor to be considered[39]. This was in the context of determining whether a substantially increased cost could be justified given that the two drugs have similar levels of efficacy in preventing falciparum malaria, that doxycycline was reasonably well tolerated, and that it offered additional benefits in protecting against other tropical diseases. It was subsequently determined that there was no compelling reason to switch from doxycycline to atovaquone/proguanil for first line prevention of malaria.

Supply of antimalarials on operations

103. The Committee has heard varying accounts regarding how antimalarials were provided on deployment, both in general and during the studies. The requirement to take antimalarial medications on operations is part of an overall force protection plan. It is detailed either in a stand-alone Health Support Plan or, in the case of large Operations, in an annex to the overall Operations Order. These force protection measures are not optional. It is standard practice for a medical officer to produce a prescription for the medication required by each individual. Dispensing of the medication for the initial period of an operation is usually conducted at the supporting health centre pharmacy. Depending on the nature and length of the deployment, members may be provided with enough medication to last the entire period, however, this is often not the case for longer deployments for logistical reasons.

104. For prolonged operations medications, including antimalarials, are usually supplied to the supporting health element and distributed by health personnel, including medics, during the deployment. Due to the requirement for doxycycline to be taken with food and at the same time each day, it has sometimes been distributed by embedded health personnel in bowls placed on tables at meal times. This also helps maintain access to medications for those who find themselves in an unplanned location without their antimalarial medication.

105. Distribution of medications to those participating in the studies followed these general guidelines. Due to the high level of scrutiny involved with conducting the studies, it is understood that often the antimalarial medications were given out weekly by medics ‘on parade’ to ensure compliance, rather than each individual being given a longer term supply of the medication.

106. If members are changed from one medication to another during a deployment due to side-effects or intolerance to the initial medication, it is standard practice for this to be prescribed by a

[37] For example Submission 17 to the Inquiry by the Quinism Foundation.
[38] This was a double-blinded pre-registration study of atovaquone/proguanil to determine its tolerability and efficacy in a deployed military population (Elmes N, Bennett S, Nasveld, P. *Malaria in the Australian Defence Force: the Bougainville experience.* ADF Health, 2004, 5 (2). pp. 69-72)
[39] Elmes N, Bennett S, Nasveld, P. *Malaria in the Australian Defence Force: the Bougainville experience.* ADF Health, 2004, 5 (2). pp. 69-72.

medical officer and for a note to be placed in the member's medical record. The required medications would then be dispensed from the supporting health element.

Duration of mefloquine use for prevention of malaria

107. The Committee has heard concerns from veterans that the use of mefloquine for prolonged periods (greater than three months) contradicts the advice of the manufacturers. Drug registration bodies initially license drugs based on the studies presented to them and most antimalarial drug studies are conducted for less than six months for logistical reasons. The Product Information for mefloquine now states that "This drug has been administered for longer than 1 year. If the drug is to be administered for a prolonged period, periodic evaluations including liver function tests should be performed."[40] The United States Centers for Disease Control and Prevention (CDC) places no recommended time limits on the duration of use of mefloquine for the prevention of malaria[41].

108. Mefloquine had been successfully used for long periods in Africa by the US Peace Corps prior to the Timor-Leste studies with no evidence of long term health effects[42]. Long term follow-up of the US Peace Corps, a majority of whom took mefloquine, showed no serious adverse effects attributable to the medication after more than 10 years[43].

[40] Roche. *Product and Consumer Medicine Information Licence, Lariam ®, Mefloquine Hydrochloride* (Australia).
[41] See CDC Fact Sheet at: https://www.cdc.gov/malaria/resources/pdf/fsp/drugs/mefloquine.pdf
[42] Lobel HO, Campbell CC, Hightower AH, et al. Long-term malaria prophylaxis with weekly mefloquine. The Lancet. 1993 Apr 3;341(8849):848-51
[43] Tan KR, Henderson SJ, Williamson J, et al. Long term health outcomes among Returned Peace Corps Volunteers after malaria prophylaxis, 1995–2014. Travel medicine and infectious disease. 2017 May 1;17:50-5.

SIDE EFFECTS, DIAGNOSIS AND TREATMENT

109. Over the course of this Inquiry, the Committee has heard much about the short and perceived long term side effects of mefloquine and tafenoquine from those who took the medications. Many tragic accounts have been heard from former ADF members who are suffering from a variety of long term health, including mental health, problems. This is of great concern to Defence and is why Defence continues to encourage any individual or their family to seek care - whatever the cause - whether it be from ADF health facilities or from DVA or the Veterans and Veterans Families Counselling Service (VVCS).

110. In light of this, the Committee has asked for more information about the process of making a diagnosis in those who have long term symptoms they believe may be related to these medications[44].

Short term effects – vivid dreams

111. As reported to the Committee by many individuals, mefloquine has been shown to cause vivid dreams in some people. This is generally regarded as a mild event without long term consequences, and is not in itself regarded as a reason to cease the medication.

112. Dreaming, including having vivid dreams, is a common event. It occurs predominantly in Rapid Eye Movement (REM) sleep, and tends to increase in duration as the night goes on. People are most likely to remember the last dream that they have in the sleep cycle. The last dream in the sleep cycle is often also the longest and most vivid.

113. Many medications are known to cause vivid dreams, including blood pressure medications, beta blockers, some medications for Parkinson's disease, some medications for smoking cessation, and antidepressants. Vivid dreams can also be more common in individuals who have disrupted sleep, anxiety, stress, and changes to sleep schedule (changes to time zones and shift work), many of which can occur on deployments.

114. Vivid dreams have been reported when using tafenoquine but at similar rates to those taking a placebo in non-deployed subjects. The rates in the ADF studies were higher and this implies that deployment related factors may have been involved.

115. It should be noted that some soldiers describe "doxy dreams" despite this not being noted in the Product Information for doxycycline. These are much more likely to be related to deployment related factors rather than the medication itself, as it is not described as a common effect in general population studies.

Long term effects

116. While the Committee has heard from a large number of individuals who have serious long term health effects, what has not been clearly established is the cause of these health problems. Indeed, while Defence has never denied that long term problems have been attributed to the use of mefloquine, the evidence would suggest that this is rare. There is no compelling evidence that tafenoquine causes long term effects; however advocates have suggested that it may do based on findings in earlier medications from the same class of drugs - a form of 'guilt by association'. There are many possible causes for the symptoms that those who have presented to the Inquiry are

[44] Senate Foreign Affairs, Defence and Trade References Committee. Use of the quinolone antimalarial drugs mefloquine and tafenoquine in the Australian Defence Force. Brisbane Public Hearing, 30 August 2018 p 24

experiencing; however, the evidence suggests that it is far more likely that they are related to exposure to traumatic events than the use of antimalarials.

Trauma related symptoms

117. In its submission to the FDA, GSK made specific note of the late reports of neuropsychiatric symptoms in ADF personnel, which were made more than 15 years after the studies and at a rate higher than during the studies themselves[45]. It noted that these reports were not medically confirmed, but were at a higher rate than those seen in non-military populations. The submission noted that data limitations and factors such as recruitment, selection and recall bias made it impossible to make a connection between the mild to moderate side-effects reported at the time of the studies, and the permanent and serious health effects being reported many years later. The observation was made that "(T)the majority of soldiers making reports were exposed to triggers for post-traumatic stress syndrome, the symptoms of which are similar to those included in the (later) reports"[46] and that "…it is possible that deployed ADF soldiers represented a higher risk population" than the other populations studied. This does not mean that the neuropsychiatric symptoms reported were causally related to the drug, only that they were reported at higher rates than other populations that took this drug.

118. Like the GSK submission, the submission by 60P noted that the ADF tafenoquine prevention study group had a unique psychiatric adverse event profile compared to all other tafenoquine prevention studies[47]. In attempting to explain this discrepancy, the submission references a number of studies that have shown that deployment is itself a risk factor for neuropsychiatric events, dating back to at least the US Civil War. In almost all of these studies, a suitable control population is unavailable. It notes that recent studies that do report on comparisons between deployed and non-deployed personnel, or between pre- and post-deployment mental health status, strongly support a negative effect of deployment on mental health. Their conclusion was that, due to this background level of outcomes, attribution of these symptoms to tafenoquine was "…not plausible"[48].

119. As mentioned in Defence's submission, the deployment to Timor-Leste was not a benign environment and was declared as warlike service by the Australian Government. A comprehensive study of personnel who deployed to Timor-Leste was conducted in 2007[49]. The study estimated that 7.2 per cent of personnel who deployed to Timor-Leste self-reported symptoms of PTSD, and that 6.9 per cent had a high level of psychological stress in the long term. This was based on data gathered seven to nine years after deployment. In the study a number of specific traumatic exposures were reported by deployed ADF personnel including:

a. danger of being injured or killed (reported by 71 per cent of ADF members)

b. witness to human degradation and misery on a large scale (58 per cent)

c. seeing dead bodies (49 per cent) or handling dead bodies (28 per cent)

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[45] The GSK briefing to the FDA is available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM612875.pdf

[46] Ibid p 26

[47] The 60P briefing to the FDA is included in Submission 9 to this Inquiry and is available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM614202.pdf

[48] Ibid p 124

[49] Waller M, Treloar SA, Sim MR, McFarlane AC, McGuire ACL, Bleier J, Dobson AJ. Traumatic events, other operational stressors and physical and mental health reported by Australian Defence Force personnel following peacekeeping and war-like deployments *BMC Psychiatry*201212:88

d. fear of exposure to a toxic agent, contagious disease, or injury (31 per cent)

e. hearing of a close friend or co-worker injured or killed (30 per cent)

f. being present when a close friend or co-worker was injured or killed (13 per cent)

g. other stressors, including threat of danger (67 per cent) and health concerns (52 per cent)

120. If you were to extrapolate these figures to those who took mefloquine or tafenoquine as part of the antimalarial studies (2859), it could be expected that over 200 personnel in this group may have had symptoms of PTSD at the time of the 2007 study, and just under 200 would have had a high level of psychological stress in the long term. The prevalence of PTSD in military cohorts has also been shown to increase over time therefore these rates could be even higher amongst this group[50]. Such evidence makes it very difficult to ascribe a specific, non-trauma related cause to those who are now experiencing symptoms of mental health conditions.

121. A newly published study that examined nearly 20,000 US veterans from South-West Asian deployments (Iraq and Afghanistan) between 2001and 2008 supports the premise that long term adverse effects are more likely to be related to deployment experiences than antimalarials[51]. The study demonstrated no significant mental health adverse outcomes related to antimalarial medications when combat exposure was taken into account[52]. The deployed veterans group was compared against a non-deployed group who had also taken antimalarial medications. No significant associations were found between mefloquine use and mental health and physical health outcomes. The study outcomes concluded that combat and deployment experiences are potent factors associated with mental health outcomes, independently of other recognised hazards such as medication side effects. Although the findings suggested that veterans' mental health morbidity is not a result of mefloquine or other preventive medications, the researchers acknowledged that further research is warranted.

Acquired Brain Injury

122. Several individuals have postulated that mefloquine and tafenoquine have a neurotoxic effect (i.e. that it damages the brain) and can cause an acquired brain injury. The term 'acquired brain injury' (ABI) is a generic term that covers any brain injury that occurs after birth. Causes include traumatic brain injury or concussion, stroke, drugs, alcohol, degenerative brain conditions such as Alzheimer's Disease, and poisons. As the Committee has heard, the hypothesis that mefloquine and tafenoquine cause ABI is not backed by definitive evidence[53].

[50] For example, in a more recent study of individuals who had transitioned from ADF service between 2010 and 2015, 24.9 per cent were estimated to meet diagnostic criteria for PTSD. Van Hooff M, Lawrence-Wood E, Hodson S, Sadler N, Benassi H, Hansen C, Grace B, Avery J, Searle A, Iannos M, Abraham M, Baur J, McFarlane A. *Mental Health Prevalence, Mental Health and Wellbeing Transition Study*, The Departments of Defence and Veterans' Affairs, Canberra. 2018

[51] Schneiderman AI, Cypel YS, Dursa EK, Bossarte RM. Associations between Use of Antimalarial Medications and Health among U.S. Veterans of the Wars in Iraq and Afghanistan. Am. J. Trop. Med. Hyg., 99(3), 2018, pp. 638–648

[52] Combat exposure was measured by the use of three survey questions: "Did you ever feel that you were in great danger of being killed?"; "Did you see anyone wounded, killed or dead?"; "Were you engaged in direct combat where you discharged your weapon?"

[53] For an independent analysis of this hypothesis see Submission 15 by Associate Professor Karunajeewa, pp. 6-8.

123. Diagnosing an ABI can be difficult as there are many causes and many similarities between its symptoms and those of mental health conditions. As Mr Stuart McCarthy said in his evidence to the Committee ABI is "…a diagnosis of exclusion, which can be very difficult and very challenging" [54]. A diagnosis of exclusion involves the elimination of other reasonable possibilities. It generally occurs when scientific knowledge is scarce, or where the means to verify a diagnosis by objective means is absent. Several of the individuals who have provided evidence to the Inquiry have revealed that they already have diagnoses made by specialists according to established criteria. While individuals may disagree with their diagnosis this does not justify its dismissal in the search for an alternative and controversial one that is not backed by scientific evidence. As discussed in Defence's submission, another explanation could be that an alternative diagnosis or explanation of their condition that may be less stigmatising and easier for them and others to accept.

124. As detailed in Defence's submission, in August 2017 the independent Repatriation Medical Authority (RMA) found that there was insufficient sound medical-scientific evidence to determine that exposure to mefloquine, tafenoquine or primaquine causes chronic brain injury.
On 17 September 2018 the Specialist Medical Review Council (SMRC) released the outcomes of its review into this matter and upheld the decision of RMA not to create Statement of Principles (SOPs) for chemically-acquired brain injury related to mefloquine or tafenoquine[55]. In its determination the Council stated that it "...was not satisfied on the balance of probabilities that "chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine" is a particular kind of injury or disease within the meaning of the VEA". These two findings confirm that the link between mefloquine and tafenoquine and ABI has not been identified.

Diagnosing and treating symptoms thought to be related to antimalarials

125. The approach to diagnosing symptoms that develop while taking a medication is relatively straight forward. The doctor takes a detailed history of the type of symptoms experienced, when they occurred, and what other factors may be involved. If the symptoms are thought to be related to a medication it is stopped to assesses whether the symptoms resolve. This is also true for mefloquine and tafenoquine. While persistence of symptoms after taking mefloquine has been reported, in the vast majority of cases symptoms cease when the medication is stopped.

126. An independent review of the published literature on the neuropsychiatric effects of mefloquine concluded that there is no specific way to diagnose whether long term symptoms are related to mefloquine[56]. The independent review also concluded that there is no specific treatment for perceived long term effects of mefloquine except to treat the symptoms, which can resemble those of other health conditions[57].

[54] Senate Foreign Affairs, Defence and Trade References Committee. Use of the quinolone antimalarial drugs mefloquine and tafenoquine in the Australian Defence Force. Brisbane Public Hearing, 30 August 2018, p 8
[55] Specialist Medical Review Council. Re: Decision of the Repatriation Medical Authority not to make Statements of Principles for "chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine". Request for Review Declaration No. 34. Commonwealth of Australia Gazette. 17 September 2018
[56] McFarlane AC. Neuropsychiatric effects of Mefloquine: Literature Review for Joint Health Command. 2016. A copy of the review was provided at Annex K of Defence's submission to the Inquiry and is available at: http://www.defence.gov.au/Health/HealthPortal/Malaria/Documents/Literature%20Review.pdf
[57] McFarlane AC. Neuropsychiatric effects of Mefloquine: Literature Review for Joint Health Command. 2016.

127. Defence notes than several individuals who have provided information to the Inquiry are seeking specialist review, treatment and rehabilitation. There are no medical specialists that specifically specialise in the diagnosis and treatment of long term symptoms believed to be related to having taken mefloquine. This is understandably difficult for individuals to accept, but reassuringly, the cause of the symptoms does not necessarily determine therapy, and they can still seek and be provided assistance for their current health problems based on the symptoms they are experiencing.

128. On this basis, Defence developed and released clinical guidelines for Defence general practitioners (GPs) for the management of members who are concerned about mefloquine in 2016[58]. This has been promulgated throughout Defence, is available on the ADF Malaria webpage, and has been shared with DVA, who further promulgated it to civilian GPs. These guidelines emphasise that individuals who are concerned should be treated with respect, even if it is unlikely that their symptoms have been caused by mefloquine. The steps in management are as follows:

a. Document all symptoms.

b. Examine the patient, including specific neurological testing.

c. Assess the patient with readily available psychological screens, if relevant.

d. Arrange further diagnostic investigations or specialist referral as appropriate (based on symptoms). If the individual has neurological symptoms, consider referral to a neurologist, and/or a neuropsychologist, including a request to undertake baseline neuropsychological function. Individuals presenting with mental health symptoms should be referred to a psychiatrist, preferably a psychiatrist with experience in military mental health.

e. Assess and document risk (to self or others).

f. Explore useful treatments. Treatment options will depend on the symptoms being experienced and whether a condition can be diagnosed.

129. The guidelines note that, where a clinical diagnosis is made, evidence based treatment for the condition should be provided but that no specific treatment has been proposed for mefloquine-related neuropsychiatric problems except to cease the medication. They also advise that treatment with medications (pharmacotherapy) or psychotherapy should be withheld until a disorder is diagnosed, however treatment of specific symptoms causing significant distress should be considered even without a diagnosis.

130. The fact is that, even if a causal link between the use of these medications and the current symptoms that individuals are experiencing could be established, this is unlikely to alter the individual's treatment or management program. Defence's advice to all those who believe they are having long term symptoms relating to the use of either of these medications, or indeed symptoms of any kind, is to see their treating doctor and discuss it with them, utilising these guidelines as appropriate.

[58] See Annex M to Defence's submission to the Inquiry

Other considerations

131. There is no doubt that many of those who have made a submission to the Inquiry believe that their symptoms have been caused by these medications and this is not in dispute. As Professor Brown stated in his testimony to the Brisbane public hearing:

> *…it is a fact that some people believe their long-term symptoms are related to ingestion of mefloquine. And it is a fact that the majority of experts in the field do not believe there is an evidence based basis to make this assertion at this stage*[59].

132. These two conflicting facts have created a hostile public discourse and made it extremely difficult for Defence and DVA to provide assistance to those in need. Some veterans' fixation on a mistaken understanding of the cause of their mental health problems has inhibited them from accepting the medical help that is available. Many of those providing evidence to the Inquiry have stated that they have been diagnosed with PTSD but are frustrated that treatment does not seem to be working. The failure of some people diagnosed with PTSD to improve is a known problem, but it does not necessarily mean that the diagnosis is wrong. The public discourse has also perhaps adversely influenced other veterans who had not previously thought that their long term mental health problems were due to antimalarial drugs taken 20 years ago.

133. One of the more troubling aspects for Defence is that individuals with diagnosed mental health conditions are perhaps being further harmed by the mistaken public commentary surrounding these drugs. There is emerging research that suggests that those who transition from Defence experience high rates of mental health problems[60]. While some of this is related to specific traumatic events experienced while serving in the military, another factor may be that they have left the security and support of the Defence environment and, in effect, their ADF 'family'. The false narrative repeated by many advocates around Defence's use of mefloquine and tafenoquine is that this family 'betrayed' them – by allegedly experimenting on them without consent or even 'poisoning' them. This could have further negative impacts on their health and make it even more difficult for Defence and DVA to engage and help these people.

[59] Senate Foreign Affairs, Defence and Trade References Committee. Use of the quinolone antimalarial drugs mefloquine and tafenoquine in the Australian Defence Force. Brisbane Public Hearing, 30 August 2018, p 47

[60] Van Hooff M, Lawrence-Wood E, Hodson S, Sadler N, Benassi H, Hansen C, Grace B, Avery J, Searle A, Iannos M, Abraham M, Baur J, McFarlane A. *Mental Health Prevalence, Mental Health and Wellbeing Transition Study*, The Departments of Defence and Veterans' Affairs, Canberra. 2018

ASSISTANCE TO CURRENT AND FORMER SERVING MEMBERS

134. The Committee has heard from several individuals of their opinion that Defence and DVA have failed to provide assistance to those who believe they have been affected by antimalarial medications. The Committee has also heard that Defence has failed to acknowledge the concerns of these individuals and has expressed some confusion over the apology issued by the Surgeon General Australian Defence Force (SGADF) in 2016.

135. Both Defence and DVA have offered multiple opportunities to communicate with concerned current and former serving members, and provided specific avenues for them to access assistance and/or information. From Defence's perspective this has included: participating in various forums including DVA outreach activities; the creation of comprehensive webpages; establishment of a dedicated contact email address; publication of a number of internal Defence communications; and development of management guidelines for GPs. All outreach activities have been carefully calibrated to ensure those with concerns can access information that might assist them to seek support while not causing undue alarm to others.

136. More clarification on some of the specific aspects raised in the Inquiry are provided below.

Provision of information by Defence

137. Several former serving members have been critical of Defence's provision of study records and the assistance provided to them by Defence.

138. Defence has now responded to well over four hundred requests for information and/or study records from current and former serving members. The study records themselves were stored in paper form and held at ADFMIDI and had to be located, scanned, and reviewed by a medical officer before release. In order to ensure that former serving members have all the information they require, Defence often has to request the member's medical documents from Defence Archives, a process that itself can take several weeks. The medical officer then prepares a covering letter for the documents, which provides additional information and clarification regarding what the records show. Each letter is then personally reviewed and signed by the SGADF to ensure that all possible assistance is being provided.

139. The above process is time consuming and it is acknowledged that there were delays in providing information in the first few months of the process being established due to the large volume of initial requests. This backlog has now been addressed, in part because all study records have now been professionally digitised.

140. Some individuals who have been provided a response express dissatisfaction regarding the information they have received. If this is the case, every possible effort is made to understand their concerns and provide them further clarification. A small number have specifically asked Defence to provide treatment or referral to a specialist. Defence cannot provide this service for former serving members, however information is provided on how to seek assistance through DVA.

141. As detailed in the Defence submission, a large number (approximately 25 per cent) of concerned individuals who have emailed the Defence adf.malaria@defence.gov.au mailbox in search of their study records or confirmation of study participation were not in a study. Despite Defence's best efforts to provide proof of this fact, some individuals remain frustrated and have accused Defence of lying or "covering up" information.

142. An example of this is the concern expressed by the parents of Jacqueline Davies at the Townsville public hearing[61]. The SGADF met Mrs Davies at the Townsville Forum in March 2016 and offered to assist her in obtaining her daughter's health information. Numerous email exchanges occurred over the following months, during which it was confirmed through documentation that Jacqueline was not on any of the antimalarial studies, had in fact taken doxycycline during her deployment, and that there was no evidence that she had ever taken mefloquine while serving in the ADF.

Apology by SGADF

143. Discussion occurred at the Inquiry's Townsville public hearing as to whether Defence has acknowledged that mefloquine has been shown to have long term effects and whether an apology provided by the SGADF was related to this acknowledgement[62]. Defence has acknowledged since at least the March 2016 Townsville forum that, as shown in the international literature, mefloquine can cause long term health effects in a small number of individuals. However, neither Defence nor SGADF has issued a blanket formal apology for its use of mefloquine and tafenoquine, as there is no evidence that this use has been either unethical or inappropriate.

144. A limited apology was provided in the United Kingdom (UK) during their House of Commons Defence Committee Inquiry into the use of mefloquine[63]. During testimony, the then Minister for Defence Personnel, Welfare and Veterans apologised to those former or current UK service personnel who were given mefloquine without having a face to face consultation and risk assessment with a doctor. There is no evidence that this was the case in Australia, either in the studies or for those who received mefloquine outside of the studies.

145. The SGADF has made two apologies to individuals where review of medical records have revealed errors in medical management. The case discussed at the Townsville public hearing related to an apology issued in July 2016 to a former member who was given mefloquine despite having a recorded history of a mental health condition. As indicated in the letter, as well as seeing a study doctor as part of the informed consent process, the individual also saw a separate medical officer to undergo a pre-deployment medical, who noted that he would be taking mefloquine. The fact that the former member had a past history of mental health problems should have resulted in him being excluded from the studies but this did not occur. The former member commenced on the trial but mefloquine was ceased after about a week due to reported sleep disturbances and he was switched to doxycycline.

146. An apology was issued relating to the failure to exclude the former member from the study. The letter provided an opinion that this may have occurred due to the fact that the study doctors may not have had full access to his hard copy medical record. It was noted that this would not happen today as Defence introduced an electronic Health System in 2014 making it easier for health providers to access documentation[64]. The letter also noted that it was not possible to determine whether the former member's subsequent health problems were exacerbated by mefloquine from the information available.

[61] Senate Foreign Affairs, Defence and Trade References Committee. Use of the quinolone antimalarial drugs mefloquine and tafenoquine in the Australian Defence Force. Townsville Public Hearing, 30 August 2018, pp 1-7
[62] Senate Foreign Affairs, Defence and Trade References Committee. Use of the quinolone antimalarial drugs mefloquine and tafenoquine in the Australian Defence Force. Townsville Public Hearing, 31 August 2018, p 23
[63] House of Commons Defence Committee. *An Acceptable risk? The use of Lariam for military personnel*. Fourth Report of Session 2015 – 2016, 10 May 2016, p 30
[64] Note that the Defence eHealth System (DeHS) is a closed system and is not related to the national My Health Record.

Outreach

147. Defence and DVA have considered whether further individual outreach to all those who participated in the antimalarial studies is warranted. Given that the vast majority of the individuals who participated in the studies are unlikely to have ongoing health problems, it was determined by both departments that contacting this majority would cause more harm than good, in that it may cause unnecessary worry to individuals who have no reason to be concerned. In other words if individuals do not know they have a problem, they do not need to be contacted; if they do believe that they have a problem that needs addressing, there are ways to seek support. This is why the focus of both Defence and DVA has been on providing pathways to access support for those concerned.

148. Individual follow-up is also likely to be a very resource intensive process, not least because of the difficulty associated with contacting former serving members who transitioned from Defence up to 18 years ago. It also risks diverting resources away from other programs supporting the health of current and former serving members.

149. Defence is in full agreement with the Committee that all possible assistance needs to continue to be provided to veterans, regardless of the possible cause of their symptoms. Defence continues to work closely with DVA to ensure ongoing access to care and information. It is appropriate that DVA takes the lead in this process, as the vast majority of those who were participants in the studies are no longer serving in the ADF[65].

150. Defence will support DVA in their upcoming mefloquine and tafenoquine consultation forums. The purpose of the two hour forum is to provide an opportunity to hear from current and former serving members and outline the treatments, services and supports available. This will help DVA and Defence to continue to understand the needs of those who have concerns about these medications and to direct them quickly to available treatment options.

151. DVA has also created a dedicated phone line – 1800 MEFLOQUINE (1800 633 567) - for veterans with enquiries about the upcoming consultation forums and other available support.

[65] For those who took mefloquine or tafenoquine in these studies, only approximately 14 per cent and five per cent respectively are still serving in some capacity.

CONCLUSION

152. This supplementary submission is offered in an attempt to clarify what is a difficult and complex issue. As evidence has emerged, there appear to be three key themes or areas of concern: the conduct of the studies and, to a lesser extent, Defence's more general use of mefloquine; the question of whether mefloquine and tafenoquine cause long term effects, and particularly ABI; and the need for Defence and DVA to continue to provide support to those having long term health problems, regardless of the cause.

153. Defence stands by the integrity of its approach to the use of antimalarials, including in the conduct of studies involving these medications. Defence's use of antimalarials has been consistent with, and sometimes more conservative than, that of other militaries. Its research has been conducted in accordance with international and national guidelines, under the supervision of a properly constituted Ethics Committee. The studies have been independently validated by the IGADF and a US FDA audit.

154. While it has long been acknowledged that mefloquine can cause long term health effects in a small number of individuals, independent medical authorities such as RMA and SMRC have determined that there is insufficient evidence that a causal link exists between antimalarial use and ABI to warrant a separate SOP[66]. In addition, a large study in the US Army found no significant associations between mefloquine use and mental health and physical health outcomes, and concluded that combat and deployment experiences are more likely to be the cause of adverse outcomes. In regards to tafenoquine, both the FDA and TGA were satisfied that the medication meets the appropriate safety requirements to be registered for general use.

155. Finally the most important aspect of this issue remains the health and welfare of current and former serving members. The simple message that Defence has promulgated throughout is that assistance is readily available to all those who have concerns about their health, regardless of the cause. For serving members, this is through their local Joint Health Command on-base health facility. For veterans, options include their regular GP, via the DVA mefloquine hotline or through accessing non-liability healthcare and VVCS.

156. Defence has been transparent and proactive throughout the public campaign relating to the use of mefloquine and tafenoquine. It has used best endeavours to provide concerned individuals with the information and assistance they require. Unfortunately despite these best efforts the information that has been provided, much of which has been validated by independent experts, has often been met with disbelief and mistrust, particularly from former serving members. This in turn appears to be having an adverse effect on the health of many of the individuals who were involved in the studies.

157. Defence again thanks the Committee for the opportunity to clarify its position and looks forward to answering any other questions that the Committee has on these matters.

[66] The two antimalarials are listed as potential causal factors in the SOPs for 16 conditions (15 for mefloquine and six for tafenoquine).

ANNEXES

Annex A – Product Information for Krintafel™

Annex B – Product Information for Arakoda™

Annex C –Tafenoquine prevention study (Study 033) - Study Protocol Released under FOI

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Annex A

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

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

INDICATIONS AND USAGE

KRINTAFEL is an antimalarial indicated for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection. (1)

Limitation of Use
KRINTAFEL is NOT indicated for the treatment of acute *P. vivax* malaria. (1)

DOSAGE AND ADMINISTRATION

- All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing KRINTAFEL. (2.1)
- Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with KRINTAFEL. (2.1)
- The recommended dose of KRINTAFEL in patients aged 16 years and older is a single dose of 300 mg administered as two 150-mg KRINTAFEL tablets taken together. (2.2)
- Coadminister KRINTAFEL on the first or second day of the appropriate antimalarial therapy for the acute *P. vivax* malaria. (2.2)
- Administer KRINTAFEL with food. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 150 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)
- Known hypersensitivity reactions to tafenoquine, other 8-aminoquinolines, or any component of KRINTAFEL. (4)

WARNINGS AND PRECAUTIONS

- Hemolytic Anemia: G6PD testing must be performed before prescribing KRINTAFEL due to the risk of hemolytic anemia. Monitor patients for clinical signs or symptoms of hemolysis. (5 1)
- G6PD Deficiency in Pregnancy or Lactation: KRINTAFEL may cause hemolytic anemia when administered to a pregnant woman with a G6PD-deficient fetus. KRINTAFEL is not recommended during pregnancy. A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to KRINTAFEL 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 psychiatric adverse reactions have been observed in patients with a previous history of psychiatric conditions at doses higher than the approved dose. The benefit of treatment with KRINTAFEL must be weighed against the potential risk for psychiatric adverse reactions in patients with a history of psychiatric illness. (5.4)
- Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., angioedema) have been observed with administration of KRINTAFEL. If hypersensitivity reactions occur, institute appropriate therapy. (5.5)
- Due to the long half-life of KRINTAFEL (15 days), psychiatric effects and hypersensitivity reactions may be delayed in onset and/or duration. (5.4, 5.5, 12 3)

ADVERSE REACTIONS

Common adverse reactions (≥5%) were dizziness, nausea, vomiting, headache, and decreased hemoglobin. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Avoid coadministration 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 for 3 months after the dose of KRINTAFEL. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KRINTAFEL is indicated for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection *[see Dosage and Administration (2.2)]*.

Limitation of Use

KRINTAFEL is NOT indicated for the treatment of acute *P. vivax* malaria.

2 DOSAGE AND ADMINISTRATION

2.1 Tests to be Performed Prior to Treatment with KRINTAFEL

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

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

2.2 Recommended Dosage and Administration

The recommended dose of KRINTAFEL in patients aged 16 years and older is a single dose of 300 mg administered as two 150-mg tablets taken together. Coadminister KRINTAFEL on the first or second day of the appropriate antimalarial therapy (e.g. chloroquine) for acute *P. vivax* malaria *[see Clinical Studies (14)]*.

Administer KRINTAFEL with food to increase systemic absorption *[see Clinical Pharmacology (12.3)]*.

Swallow tablets whole. Do not break, crush, or chew the tablets.

In the event of vomiting within 1 hour after dosing, a repeat dose should be given. Re-dosing should not be attempted more than once.

3 DOSAGE FORMS AND STRENGTHS

KRINTAFEL tablets are pink, film-coated, capsule-shaped tablets debossed with 'GS J11' on one side and contain 150 mg of tafenoquine.

4 CONTRAINDICATIONS

KRINTAFEL is contraindicated in:

- patients with G6PD deficiency or unknown G6PD status due to the risk of hemolytic anemia *[see Warnings and Precautions (5.1)]*.

- 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 Use in Specific Populations (8.2)]*.
- patients with known hypersensitivity to tafenoquine, other 8-aminoquinolines, or any component of KRINTAFEL *[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 KRINTAFEL *[see Dosage and Administration (2.1)]*. 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. Treatment with KRINTAFEL is contraindicated in patients with G6PD deficiency or unknown G6PD status *[see Contraindications (4)]*. Patients were excluded from clinical trials of KRINTAFEL if they had a G6PD enzyme activity level <70% of the site median value for G6PD normal activity *[see Clinical Studies (14)]*. 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. Advise patients to seek medical attention if signs of hemolysis occur.

5.2 G6PD Deficiency in Pregnancy or Lactation

Potential Harm to the Fetus

The use of KRINTAFEL 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 KRINTAFEL during pregnancy is not recommended and to avoid pregnancy or use effective contraception for 3 months after the dose of KRINTAFEL *[see Use in Specific Populations (8.1, 8.3)]*.

Potential Harm to the Breastfeeding Infant

A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to KRINTAFEL through breast milk. Infant G6PD status should be checked before breastfeeding begins. KRINTAFEL 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 for 3 months after the dose of KRINTAFEL *[see Use in Specific Populations (8.2)]*.

5.3 Methemoglobinemia

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

5.4 Psychiatric Effects

Psychiatric adverse reactions including anxiety (<1%), abnormal dreams (<1%), and insomnia (3%) have been reported in clinical trials of KRINTAFEL *[see Adverse Reactions (6.1)]*. Two cases of depression and 2 cases of psychosis have occurred primarily in patients with a history of psychiatric disorders following receipt of single doses of tafenoquine that were higher than the approved 300-mg dose (350 mg to 600 mg). Safety and effectiveness of KRINTAFEL have not been established at doses or regimens other than the approved regimen; use of KRINTAFEL at doses or regimens other than a 300-mg single dose is not approved by FDA.

The benefit of treatment with KRINTAFEL must be weighed against the potential risk for psychiatric adverse reactions in patients with a history of psychiatric illness. Due to the long half-life of KRINTAFEL (approximately 15 days), signs or symptoms of psychiatric adverse reactions that may occur could be delayed in onset and/or duration *[see Clinical Pharmacology (12.3)]*.

5.5 Hypersensitivity Reactions

Serious hypersensitivity reactions (e.g., angioedema, urticaria) have been observed with administration of KRINTAFEL *[see Adverse Reactions (6.1)]*. Institute appropriate therapy if hypersensitivity reactions occur. Do not re-administer KRINTAFEL. KRINTAFEL is contraindicated in patients who develop hypersensitivity to tafenoquine or any component of KRINTAFEL or other 8-aminoquinolines *[see Contraindications (4)]*.

Due to the long half-life of KRINTAFEL (approximately 15 days), signs or symptoms of hypersensitivity adverse reactions that may occur could be delayed in onset and/or duration *[see Clinical Pharmacology (12.3)]*. Advise patients to seek medical attention if signs of hypersensitivity occur.

6 ADVERSE REACTIONS

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

- Hemolytic anemia *[see Warnings and Precautions (5.1)]*
- 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 data described below reflect exposure to 4,129 subjects, of whom 810 received a 300-mg single dose of KRINTAFEL. KRINTAFEL was evaluated in patients with *P. vivax* malaria (n = 483) in 3 randomized, double-blind trials including a placebo-controlled trial comparing KRINTAFEL plus chloroquine (n = 260) with chloroquine alone (Trial 1), a placebo-controlled dose-ranging trial (Trial 2) (n = 57) *[see Clinical Studies (14)]*, and a hematologic safety trial (Trial 3, NCT02216123) (n = 166).

In Trial 1, in patients with *P. vivax* malaria, the most common adverse reactions reported in ≥5% of patients treated with KRINTAFEL are listed in Table 1. Patients included in the trial had a mean age of 35 (range: 16 to 79 years), were 75% male and from the following regions: 70% Latin America (Brazil and Peru), 19% Southeast (SE) Asia (Thailand, Cambodia, and the Philippines), and 11% Africa (Ethiopia).

Table 1. Selected Adverse Reactions[a] Reported in ≥5% of Patients with *P. Vivax* Malaria Receiving KRINTAFEL in a Randomized, Active-Controlled Trial (Trial 1)

Adverse Reaction	Chloroquine (n = 133) %	KRINTAFEL + Chloroquine (n = 260) %
Dizziness	3	8
Nausea	7	6
Vomiting	5	6
Decreased Hemoglobin	2	5
Headache	7	5

[a] Adverse reactions reported prior to Day 29 as subsequent adverse reactions can be confounded by recurrence of malaria or retreatment with another agent from the quinoline class.

Other Adverse Reactions Reported with KRINTAFEL

Clinically significant adverse reactions with KRINTAFEL 300-mg single dose in clinical trials (n = 810) in ≤3% of subjects are listed below:

Psychiatric Disorders: Anxiety, insomnia, abnormal dreams.

Nervous System Disorders: Somnolence.

Laboratory Investigations: Increased blood creatinine, increased blood methemoglobin, increased alanine aminotransferase.

Immune System Disorders: Hypersensitivity reactions (e.g., angioedema, urticaria) *[see Contraindications (4), Warnings and Precautions (5.5)]*.

Eye Disorders: Vortex keratopathy, photophobia.

7 DRUG INTERACTIONS

7.1 Effect of KRINTAFEL 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 KRINTAFEL 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 KRINTAFEL during pregnancy may cause hemolytic anemia in a fetus who is G6PD deficient. Treatment with KRINTAFEL during pregnancy is not recommended *[see Warnings and Precautions (5.2)]*. Available data with use of KRINTAFEL 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 KRINTAFEL 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 equivalent to 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 (equivalent to 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 KRINTAFEL. Infant G6PD status should be checked before breastfeeding begins. KRINTAFEL 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), Clinical Considerations]*.

There is no information regarding the presence of KRINTAFEL 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 KRINTAFEL and any potential effects on the breastfed infant from KRINTAFEL 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 KRINTAFEL 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 for 3 months after the dose of KRINTAFEL.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

KRINTAFEL 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 KRINTAFEL during pregnancy is not recommended and to avoid pregnancy or use effective contraception for 3 months after the dose of KRINTAFEL.

8.4 Pediatric Use

The safety and effectiveness of KRINTAFEL have been established in pediatric patients aged 16 years and older. Use of KRINTAFEL in these pediatric patients is supported by evidence from adequate and well-controlled studies of KRINTAFEL *[see Clinical Studies (14)]*.

Safety and effectiveness of KRINTAFEL in pediatric patients younger than 16 years have not been established.

8.5 Geriatric Use

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

8.7 Hepatic Impairment

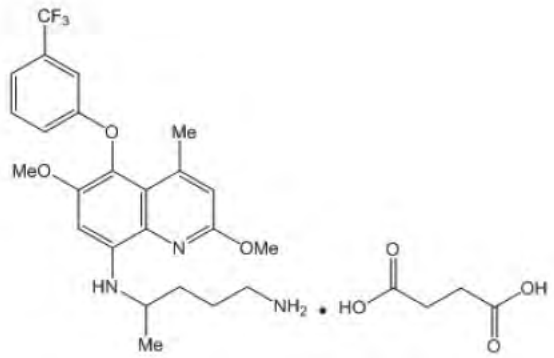
The pharmacokinetics of KRINTAFEL have not been studied in patients with hepatic impairment. If KRINTAFEL is administered to such patients, monitoring for adverse reactions associated with KRINTAFEL is needed *[see Warnings and Precautions (5), Adverse Reactions (6)]*.

10 OVERDOSAGE

Hemoglobin decline and methemoglobinemia may be encountered in an overdose with KRINTAFEL. Treatment of overdosage consists of institution of appropriate symptomatic and/or supportive therapy.

11 DESCRIPTION

KRINTAFEL contains tafenoquine succinate, an antimalarial agent for oral administration. 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 $C_{24}H_{28}F_3N_3O_3 \bullet C_4H_6O_4$, and its molecular mass is 581.6 as the succinate salt (463.5 as free base). The structural formula is shown below.



Each KRINTAFEL tablet contains 150 mg of tafenoquine (equivalent to 188.2 mg tafenoquine succinate). Inactive ingredients include magnesium stearate, mannitol, and microcrystalline cellulose. The tablet film-coating inactive ingredients include hydroxypropylmethylcellulose, polyethylene glycol, red iron oxide, 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 QTc interval was evaluated in a Phase 1 randomized, single-blind, placebo- and positive-controlled, parallel-group thorough QTc study in 260 healthy adult subjects. At a cumulative dose of 1,200 mg (400 mg/day for 3 days; 4 times the maximum recommended dose), tafenoquine did not prolong the QTc interval to any clinically relevant extent.

Exposure-Response Relationships

A saturable relationship between tafenoquine exposure (AUC) and clinical response (recurrence-free rate at 6 months) was identified. Tafenoquine exposures achieved with doses of 300 mg and higher are on the plateau of the exposure-response curve. Use of KRINTAFEL at doses or regimens other than a 300-mg single dose is not approved by the FDA.

12.3 Pharmacokinetics

Absorption

Maximum plasma concentrations were generally observed 12 to 15 hours following oral administration.

Food Effect: Plasma tafenoquine AUC increased by 41% and C_{max} increased by 31% when administered as an investigational capsule formulation with a high-calorie, high-fat meal

(approximately 1,000 calories with 15% protein, 25% carbohydrate, and 60% fat) compared with the fasted state.

Distribution

Protein binding of tafenoquine is >99.5%. The apparent oral volume of distribution is ~1,600 L. Following single- and multiple-oral-dose administration, tafenoquine whole blood concentrations were on average 67% higher than corresponding plasma values.

Elimination

The apparent oral clearance of tafenoquine is approximately 3 L/h. The average terminal half-life is approximately 15 days.

Metabolism: Tafenoquine undergoes slow metabolism. Unchanged tafenoquine represented the only notable drug-related component in human plasma after a single oral dose of tafenoquine.

Excretion: The full excretion profile of tafenoquine in humans is unknown. Over a 6-day collection period, renal elimination of unchanged tafenoquine was low.

Specific Populations

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 tafenoquine pharmacokinetics were observed following coadministration with chloroquine, dihydroartemisinin-piperaquine, or artemether-lumefantrine in healthy subjects.

No clinically significant effects on the pharmacokinetics of dihydroartemisinin, piperaquine, artemether, lumefantrine, or substrates of cytochrome P450 isoenzymes (CYP)1A2 (caffeine), CYP2D6 (desipramine), CYP2C8 (chloroquine), CYP2C9 (flurbiprofen), or CYP3A4 (midazolam, chloroquine) were observed following coadministration of tafenoquine in healthy subjects.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically: Tafenoquine inhibited metformin transport via human OCT2, MATE-1, and MATE2-K transporters. Clinical drug interaction studies with tafenoquine and OCT2 and MATE substrates have not been conducted *[see Drug Interactions (7)]*.

The effect of tafenoquine on substrates of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptides 1B1/1B3 (OATP1B1/OATP1B3) is unknown.

12.4 Microbiology

Mechanism of Action

Tafenoquine, an 8-aminoquinoline antimalarial, is active against the liver stages including the hypnozoite (dormant stage) of *P. vivax*. 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 *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, which are responsible for relapses in *P. vivax* malaria *[see Clinical Studies (14)]*.

Resistance

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

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 of 1 mg/kg/day and above (3 times the clinical exposure based on AUC comparisons). Tafenoquine was not carcinogenic in mice. Given the single-dose administration of KRINTAFEL, these findings may not represent a carcinogenicity risk to humans.

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

Trial 1 (NCT01376167) was a double-blind, controlled clinical trial of 522 adults positive for *P. vivax* across 3 regions (Asia, Africa, and Latin America). All patients received chloroquine phosphate (600-mg free base on Days 1 and 2 with 300-mg free base on Day 3) to treat the acute infection in addition to either a one-time dose of KRINTAFEL (two 150-mg tablets) on Day 1 or Day 2 (n = 260), an active control (n = 129), or placebo (n = 133) in a 2:1:1 fashion. Patients included in the trial had a mean age of 35 (range: 16 to 79 years), were 75% male and from the following regions: 70% Latin America (Brazil and Peru), 19% SE Asia (Thailand, Cambodia, and the Philippines), and 11% Africa (Ethiopia).

Patients were considered recurrence-free at 6 months if they demonstrated initial parasite clearance, took no anti-malarial medications, and were confirmed parasite-free at the 6-month final assessment (i.e., absence of relapse or new infection).

Due to the risk of hemolytic anemia, patients were excluded from the trial if they had a G6PD enzyme activity level <70% of the site median value for G6PD normals (8.2 IU/gHb). In this trial, the minimum G6PD enzyme level of any subject was 5.4 IU/gHb. Patients with severe malaria were excluded from the trial.

The recurrence-free efficacy rates at 6 months among the tafenoquine and placebo groups are presented in Table 2. The risk of recurrence for KRINTAFEL plus chloroquine was reduced by 76% compared with placebo plus chloroquine.

Table 2. Recurrence-Free Efficacy Rates of KRINTAFEL in Patients with *P. Vivax* at 6 Months – Trial 1[a]

	Tafenoquine/ Chloroquine (n = 260)	**Placebo/ Chloroquine (n = 133)**
Recurrence-free efficacy	155 (60%)	35 (26%)
Recurrence	85 (33%)	88 (66%)
Missing/indeterminate outcome	20 (8%)	10 (8%)
OR[b] (95% CI)	0.24 (0.15, 0.38)	
P value	<0.001	

[a] All randomized patients were treated and had a positive parasite smear for *P. vivax* at baseline.

[b] Odds ratio of the risk of recurrence of tafenoquine plus chloroquine versus placebo plus chloroquine using logistic regression model with treatment and region as covariates. Subjects who did not demonstrate initial clearance, took a concomitant medication with anti-malarial activity, or who had a missing Day 180 assessment were considered 'missing/indeterminate' and were counted as recurrences in the analysis.

In Trial 2 (NCT01376167), a dose-ranging trial with a study design similar to Trial 1, 57 and 54 subjects were randomized to tafenoquine 300-mg single dose plus chloroquine (same dose as in Trial 1) and placebo plus chloroquine groups, respectively. Tafenoquine plus chloroquine

demonstrated a statistically significantly higher rate of recurrence-free efficacy at 6 months compared with the placebo plus chloroquine control group (84% versus 39%, with a difference of 45% and 95% CI [29%, 61%]).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

KRINTAFEL tablets contain 150 mg of tafenoquine (equivalent to 188.2 mg tafenoquine succinate) and are pink, film-coated, capsule-shaped, and debossed with 'GS J11' on one side. KRINTAFEL is supplied as follows:

- Bottle of 30 tablets with child-resistant closure (NDC 0173-0889-13). Bottles contain a desiccant. Once opened, use within 3 months.
- Unit Dose Pack of 2 tablets in a bottle with child-resistant closure (NDC 0173-0889-39). Bottles contain a desiccant.

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].

Store in the original package to protect from moisture. Keep the bottle tightly closed and do not remove the desiccant.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

G6PD Testing and Hemolytic Anemia

Inform patients of the need for testing for G6PD deficiency before starting KRINTAFEL. Advise patients of the symptoms of hemolytic anemia and instruct them to seek medical advice promptly if such symptoms occur. Patients should contact their healthcare provider if they develop dark 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 KRINTAFEL with food to increase absorption *[see Dosage and Administration (2)]*.

Advise patients to swallow the tablet whole and not to break, crush, or chew it.

Potential Harm to the Fetus

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

Advise females of reproductive potential to avoid pregnancy or use effective contraception for 3 months after the dose of KRINTAFEL *[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 for 3 months after the dose of KRINTAFEL *[see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.2)]*.

Methemoglobinemia

Inform patients that methemoglobinemia has occurred with KRINTAFEL. Advise patients of 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 with a history of psychiatric illness regarding the potential for new or worsening psychiatric symptoms with KRINTAFEL and instruct them to seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

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

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GlaxoSmithKline

Research Triangle Park, NC 27709

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PHARMACIST—DETACH HERE AND GIVE PATIENT INFORMATION TO PATIENT

PATIENT INFORMATION
KRINTAFEL (KRIN-TAH-FELL)
(tafenoquine)
tablets, for oral use

What is KRINTAFEL?

- KRINTAFEL is a prescription medicine used to treat malaria caused by a parasite called *Plasmodium vivax* in patients aged 16 years and older who are also receiving a medicine to treat acute *Plasmodium vivax* malaria such as chloroquine.
- Malaria is a serious disease of the blood that is spread by infected mosquitos. KRINTAFEL does not work for all types of malaria.
- It is not known if KRINTAFEL is safe and effective in children younger than 16 years.

Do not use KRINTAFEL if you:

- have a blood problem called glucose-6-phosphate dehydrogenase (G6PD) deficiency (sometimes known as favism) or you have not been tested for G6PD deficiency. KRINTAFEL can cause a breakdown of red blood cells (hemolysis) in people with G6PD deficiency. Your healthcare provider will test you for G6PD deficiency before you start taking KRINTAFEL.
- are breastfeeding a child known to have G6PD deficiency or breastfeeding a child that has not been tested for G6PD deficiency.
- are allergic to tafenoquine or any of the ingredients in KRINTAFEL or if you have had an allergic reaction to similar medicines containing 8-aminoquinolines. See the end of this Patient Information leaflet for a complete list of ingredients in KRINTAFEL.

Before taking KRINTAFEL, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had mental health problems.
- are pregnant or plan to become pregnant. KRINTAFEL can harm an unborn baby who has G6PD deficiency.
- are breastfeeding or plan to breastfeed. It is not known if KRINTAFEL passes into breast milk.
  - See "**Do not use KRINTAFEL 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 while taking KRINTAFEL and for 3 months after your last dose of KRINTAFEL.
- Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. KRINTAFEL and other medicines may affect each other causing side effects.

How should I take KRINTAFEL?

- Your healthcare provider will test you for G6PD deficiency before you start taking KRINTAFEL.
- KRINTAFEL is given as 2 tablets that you take together as a single dose.
- You will take KRINTAFEL on the first or second day of your treatment with the antimalarial medicine you have been prescribed.
- Take KRINTAFEL with food to make sure the right amount of medicine is absorbed into your body.
- Swallow KRINTAFEL tablets whole. **Do not** break, crush, or chew the tablets.
- If you vomit within 1 hour of taking KRINTAFEL, call your healthcare provider as you may need to take a second dose of KRINTAFEL.

What are the possible side effects of KRINTAFEL?

KRINTAFEL can cause serious side effects, including:

- **Breakdown of red blood cells (hemolytic anemia).** Contact your healthcare provider if you develop signs of hemolytic anemia, which include darkening of the lips or urine, dizziness, confusion, feeling tired, light-headedness, or shortness of breath.
- **Hemolytic anemia in an unborn baby who has G6PD deficiency.**
  - Females who are able to become pregnant should avoid pregnancy or use effective birth control (contraception) for 3 months after the dose of KRINTAFEL. Talk with your healthcare provider about birth control methods that might be right for you.
  - Your healthcare provider will do a pregnancy test before you start taking KRINTAFEL. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with KRINTAFEL.
- **Decrease of oxygen in your blood caused by a certain type of abnormal red blood cell (methemoglobinemia).** Get medical help right away if you have darkening of the urine, nail beds, lips, or the inside of your mouth.
- **Allergic (hypersensitivity) reactions.** Serious allergic reactions can happen after you take KRINTAFEL. Allergic reactions can sometimes happen hours or days after you take a dose of KRINTAFEL. Tell your healthcare provider or get emergency help right away if you have any signs or symptoms of an allergic reaction including:
  - swelling of your face, lips, tongue, or throat
  - itching
  - trouble breathing
  - fainting, dizziness, feeling lightheaded
  - rash
  - hives

Other side effects of KRINTAFEL include mental health (psychiatric) symptoms. KRINTAFEL can cause new psychiatric symptoms including anxiety, abnormal dreams, and trouble sleeping (insomnia), or make the symptoms you already have worse. Contact your healthcare provider right away if you have new or worsening psychiatric symptoms.

The most common side effects of KRINTAFEL include: dizziness, nausea, vomiting, headache, and changes in laboratory tests for hemoglobin.

These are not all the possible side effects of KRINTAFEL.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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

General information about the safe and effective use of KRINTAFEL.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet.

Do not use KRINTAFEL for a condition for which it was not prescribed. Do not give KRINTAFEL 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 KRINTAFEL that is written for health professionals.

What are the ingredients in KRINTAFEL?

Active Ingredient: tafenoquine.

Inactive Ingredients: magnesium stearate, mannitol, and microcrystalline cellulose.

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For more information, call GlaxoSmithKline (GSK) at 1-888-825-5249.

This Patient Information has been approved by the U.S. Food and Drug Administration. Approved: July 2018

Annex B

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*

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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)]*.

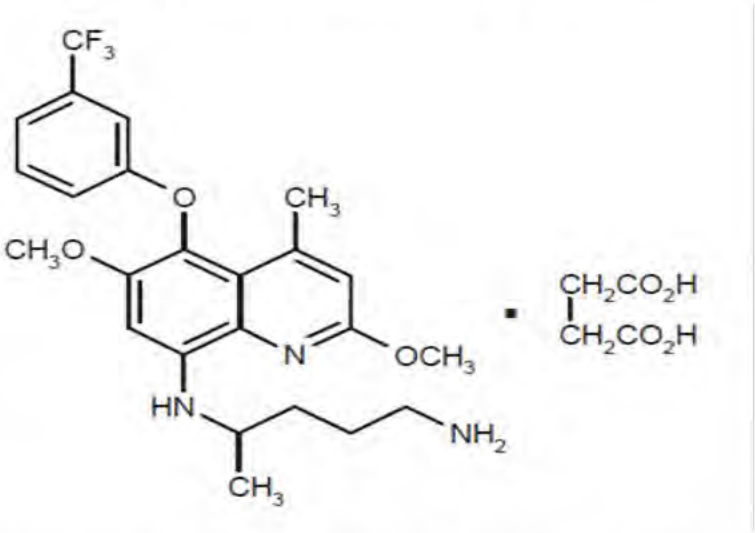
10 OVERDOSAGE

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.
  - o You should not become pregnant during treatment with ARAKODA.
  - o 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.
  - o 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:**"
  - o Your healthcare provider should check your child for G6PD deficiency before you start breastfeeding.
  - o 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

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

FOI 180/15/16
Item 2

COMMERCIAL IN CONFIDENCE

Study SB252263/033

Annex C

Final Study Report

ADHREC Protocol 216/00

Title:

A randomized, double-blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor

Report submitted by:

LtCol Peter Nasveld

Principal Investigator

09 December 2004

Title:

A randomized, double-blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor

Investigator(s):

The Principal Investigator was Lt Col Peter Nasveld. Co-investigators were Lt Col Leonard Brennan and Lt Col Michael Edstein. All investigators were from the Australian Army Malaria Institute, based in Brisbane, Australia.

Study center(s):

The study was carried out at the Lavarack Barracks, Townsville, Australia and in East Timor (at 7 sites in the Bobonaro District and in the capitol Dili)

Publication(s):

Presented at ASTMH, Denver, November 2002.

Abstract published: AM. J. TROP. MED. HYG. 2002;67(2 SUPPL.):255-256 Abs No 326.

Study Period:

The first dose of prophylactic medication was taken on 5 October 2000 and the last dose of prophylactic medication was taken on 29 April 2001. The first dose of eradication medication was taken on 31 March 2001 and the last dose of eradication medication was taken on 17 May 2001.

Phase of Development:

Phase III

Objectives:

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

The secondary study objectives were

- to assess the effectiveness of tafenoquine and mefloquine for chemoprophylaxis of *P. falciparum* and *P. vivax*,
- to assess the effectiveness of tafenoquine and primaquine in preventing post-exposure malaria,
- to characterise the population pharmacokinetics of tafenoquine and evaluate the effects of various subject characteristics on tafenoquine pharmacokinetics and
- to monitor for phospholipidosis, or effects of phospholipidosis, in man.

Methodology:

The study was divided into two phases. The first phase ('prophylactic phase') consisted of a 26 week (± 4 weeks) period where subjects received prophylactic study medication (tafenoquine or mefloquine in a ratio of 3:1). This phase was randomised, double-blind and double-dummy and compared the safety, tolerability and effectiveness of weekly regimens of the two drugs for the prophylaxis of malaria. It took place during a military deployment of the Australian Defence Force (ADF) to East Timor. Subjects who met the eligibility criteria were randomised to receive a loading dose of either tafenoquine 200 mg or mefloquine 250 mg per day for three days, followed by study treatment (tafenoquine 200 mg or mefloquine 250mg) once a week throughout the period of deployment.

Those subjects who completed the prophylactic phase entered a 24-week 'relapse follow-up phase'. At the end of the deployment, once the subjects had returned to barracks in Townsville, Australia, they received a 14 day double-blinded eradication regimen. Those who took mefloquine during the prophylactic phase received primaquine 15mg bd, whilst those who had taken tafenoquine received placebo capsules twice daily during this period. The 'relapse follow-up phase' took place in Australia, after subjects had returned to their normal duties. This phase was designed to monitor the effectiveness of tafenoquine and primaquine in preventing post-exposure relapse of malaria. Subjects were followed up over 12 weeks (for safety) involving 2 visits, followed by a further 12 weeks (for malaria relapse) involving 2 further visits or contact by telephone.

Number of subjects:

It was planned that 632 subjects would be randomised in a 3:1 ratio; i.e. 474 subjects in the tafenoquine group and 158 subjects in the mefloquine group.

Diagnosis and main criteria for inclusion:

Subjects were to be healthy, as defined by Medical Class 1 or 2 (Australian Army standard), of either sex and aged between 18 and 55 years inclusive.

Subjects with demonstrated G6PD deficiency, a history of allergy or intolerance to study medication, a history of psychiatric disorders and/or seizures, or a history of drug or alcohol abuse were to be excluded. In addition subjects with clinically significant medical history, concurrent conditions, or laboratory test results were also to be excluded.

Treatment administration:

Subjects received a loading dose of either tafenoquine 200 mg or mefloquine 250 mg per day for three days, followed by study treatment (tafenoquine 200 mg or mefloquine 250mg) once a week throughout the period of deployment.

At the end of the prophylactic phase, subjects received twice daily primaquine 15mg, or twice daily placebo, for 14 days. Those who took mefloquine during the prophylactic phase received primaquine, whilst those who had taken tafenoquine received placebo this period.

Batch nos: N99354 (tafenoquine); N00061(tafenoquine-placebo); N00212 (mefloquine); N99330 (mefloquine-placebo); N00223, N00228 (primaquine); N00061 (primaquine-placebo).

Criteria for evaluation:

Efficacy

The primary efficacy variable was prophylactic outcome (success/failure) during the prophylactic phase, up to and including the first day of eradication medication.

The subjects were monitored for any clinical signs and symptoms of malaria at each visit. In addition, blood smears were taken at baseline and at each visit during the prophylaxis phase. During the relapse follow-up phase subjects were to report any clinical signs or symptoms of malaria, at which time a blood smear was to be taken.

Prophylaxis success/failure were defined as follows:

Prophylactic Success: No clinical malaria (single positive smear with concurrent clinical signs and symptoms consistent with malaria infection) during prophylactic study drug administration up to and including the day of the first dose of eradication medication.

Prophylactic Failure: Clinical malaria (single positive smear with concurrent clinical signs and symptoms consistent with malaria infection) during prophylactic study drug administration up to and including the day of the first dose of eradication medication.

The secondary efficacy variables analysed were:

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

Planned analyses involving occurrence of clinical malaria and a single positive smear (*P. falciparum* only and *P. vivax* only) were not performed as there were no subjects with clinical malaria or a positive smear during prophylactic treatment.

Malaria prevalence at the time of the study was estimated by performing a cross-sectional survey and an entomology study. Published data sources were used to support this evidence.

Safety

Adverse events were collected at each visit during the prophylactic phase and the relapse follow-up phase. Blood was taken for haematology and clinical chemistry analysis at baseline, at each visit during the prophylactic phase and at the 12 week visit of the relapse follow-up phase.

In order to assess any phospholipidosis effects, more detailed safety assessments were carried out in a sub-group of approximately 100 subjects. These examinations included ophthalmic examination, lung function assessment, electron microscopy of peripheral blood lymphocytes and methaemoglobin assessment. ECGs were also performed to assess any effect on QTc interval.

As a result of laboratory findings in this study and across the tafenoquine program, a long-term renal follow-up was conducted in a cohort of subjects with serum creatinine concentrations ≥0.02mmol/L above baseline at the end of the end of the prophylactic phase and/or at follow-up.

Pharmacokinetics

Blood samples for assessment of plasma drug levels were collected at day 2 and weeks 4, 8, 16 and 26 of the prophylactic phase. Any subject diagnosed with clinical malaria during the prophylactic phase would have two additional samples taken: one at the time of diagnosis and the second after 12 weeks of follow-up.

The pharmacokinetics results from this study will be pooled with those from other phase III studies, and will be reported separately.

Statistical methods:

Principal Analysis (Per Protocol Population): Treatment groups were compared for prophylactic outcome by calculating the difference in the proportion of prophylactic failures (tafenoquine-mefloquine) with a 95% confidence interval (CI). The CI was calculated for the difference in two binomial proportions using standard normal approximation theory. A conclusion of non-inferiority of tafenoquine was to be drawn if the upper limit of the CI was no more than 10%. As many subjects did not stay with the company to which they had originally been allocated, the analysis stratified by Company was not performed. The primary analysis was based on all species of malaria parasitaemia.

Confirmatory Analyses: These were carried out using (i) the intent-to-treat (ITT) population and (ii) a worst case analysis in which subjects withdrawing during the prophylactic phase were included as failures. A planned covariate analysis to investigate the effect of weight was not performed because there were insufficient failures in this study.

Analysis of Secondary Efficacy Variables: For secondary variables involving numbers of subjects, treatment differences in proportions with 95% CIs were calculated: for time to event variables, Kaplan-Meier curves were produced showing cumulative survival rates.

Summary:

Subject disposition and demographic data

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

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

As expected from this military population, the majority of subjects were young white males. The majority of subjects in the study were male; 478/492 (97.2%) in the tafenoquine group and 154/163 (95.1%) in the mefloquine group. Tbe mean age was 25.4 yrs in the tafenoquine group and 26.0 years in the mefloquine group. The overall age rage was 18-51 years. The majority of subjects (>98%) were white, with <1% subjects in each group of Australian aboriginal or Pacific island origin.

The demographic characteristics of the per protocol population were similar to the overall population. The sub-group of subjects selected for additional safety assessments consisted of 98 subjects; 77 in the tafenoquine group and 21 in the mefloquine group. The mean age for this group was slightly lower (23yrs) than the overall population and all these subjects were male.

Overall, 2.5-3% of subjects had a history of malaria, with 0.6-1.8% reporting an attack in the last 6 months. As expected, the mean duration of deployment was 26-27 weeks. Some subjects left East Timor temporarily for Relief out of Country Leave (ROCL), so the mean time spent in east Timor was just under 26 weeks.

All subjects were to receive ivermectin as standard pre-deployment to prevent lymphatic filariasis. Ivermectin was also given post-deployment, as well as albendazole (standard post-deployment anti-helminthic treatment). Apart from this, the most common medications taken during the study were paracetamol and codeine.

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

Efficacy

Primary Endpoint: The principal efficacy analysis was based on the per protocol population and the ITT population was used to confirm the findings of the principal analysis.

No subjects in either treatment group developed malaria during the prophylactic phase of the study, as shown below:

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

Assumed success = no malaria during participation in the study for subjects withdrawn during prophylactic phase

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

Secondary Endpoint: Prophylactic outcome for each treatment group during prophylactic treatment plus relapse follow-up phases is summarised below:

Population	Per protocol population		Intent to treat population	
	Tafenoquine + Placebo	Mefloquine + Primaquine	Tafenoquine + Placebo	Mefloquine + Primaquine
	N=462	N=153	N=490	N=161
Prophylactic success (total)	458 (99.1%)	152 (99.3%)	486 (99.2%)	160 (99.4%)
Prophylactic success (known)	458 (99.1%)	152 (99.3%)	469 (95.7%)	156 (96.9%)
Prophylactic success (assumed)	0	0	17 (3.5%)	4 (2.5%)
Prophylactic failure	4 (0.9%)	1 (0.7%)	4 (0.8%)	1 (0.6%)
Treatment difference (tafenoquine-mefloquine)	0.21		0.20	
95% CI	-1.32, 1.74		-1.26, 1.65	

In the per protocol population, there were 4/462 (0.9%) subjects who developed malaria in the tafenoquine group and 1/153 (0.7%) subjects who developed malaria in the mefloquine group. All were cases of *P. vivax* malaria occurring during the relapse follow-up phase. There were no differences between the groups and there were no reports of mixed species malaria infections. Similar results are seen for the intent to treat population.

All the subjects who developed malaria were positive for *P. vivax* during the relapse follow-up phase. The four tafenoquine subjects all received their last dose of study medication on leaving the endemic area. The mefloquine subject received their last dose of study medication 3 days before leaving the endemic area.

Evidence of malaria prevalence during the study period is given below:

1. A cross-sectional survey was conducted in the indigenous population, in seven separate sites in the Bobonaro district close to where study subjects were deployed. Results showed that malaria (*P.falciparum* and *P.vivax*) was prevalent in 6 of the 7 sites studied during both phases of the survey.
2. Data has been published from previous ADF deployments. Troops were routinely given doxycycline or mefloquine during deployment and treated with primaquine as terminal prophylaxis. Six months after 5500 ADF troops had returned to Australia, 267 malaria infections had been reported (5%). One third of infections were first reported during deployment (mostly *P.falciparum*) while two thirds were *P.vivax* infections which became symptomatic after return to Australia. More recent data suggests that malaria continues to be a problem for Australian troops stationed in East Timor.
3. Mosquitoes were collected during their night biting phase from ADF installations and from local bodies of water. In fact (due to resource constraints) only 5% of the planned mosquito collection was performed. Of 277 *Anopheles barbirostris* collected (known to be a malaria vector), 1 was found to be positive for both *P.falciparum* and

P.vivax sporozoites. The low mosquito collection rate means that it is not possible to estimate the level of transmission from these data.

4. Weekly WHO epidemiological bulletins detail reports of malaria cases from 13 districts of East Timor. Data from bulletins from week 41 2000 to week 17 2001 (the period of the study) show that across East Timor, there was a gradual increase in cases from 598 in w41/2000 to 3063 cases in w16/2001.

5. In this study a small number of subjects in each treatment group developed post-exposure *P.vivax* malaria between 7-24 weeks after returning from the endemic area. While it is impossible to calculate a malaria attack rate from this information, it does indicate that the study population was exposed to malaria parasites.

This evidence suggests that troops in this study were exposed to malaria and protected by tafenoquine and mefloquine.

Safety

The most commonly reported adverse events during the prophylactic phase (occurring in ≥10% subjects in either treatment group) are shown below. The majority of events were of mild or moderate intensity and occurred for the first time within the first 8 weeks of the study.

Adverse Event	Treatment group	
	Tafenoquine N=492	Mefloquine N=162
At least one adverse event	454 (92.3%)	143 (88.3%)
Gastroenteritis	182 (37.0%)	51 (31.5%)
Injury	178 (36.2%)	49 (30.2%)
Upper respiratory tract infection	101 (20.5%)	32 (19.8%)
Diarrhoea	77 (15.7%)	30 (18.5%)
Back pain	74 (15.0%)	26 (16.0%)
Rash	70 (14.2%)	21 (13.0%)
Headache	61 (12.4%)	20 (12.3%)
Arthralgia	55 (11.2%)	18 (11.1%)

In general the incidence and nature of adverse events during the prophylactic phase was similar across the two treatment groups. The most common adverse events were gastroenteritis and injury. The incidence of injury is consistent with that expected in a study in active service military personnel.

During the relapse follow-up phase, 203/492 (41.3%) subjects in the tafenoquine group and 53/162 (32.7%) subjects in the mefloquine group reported an adverse event. With the exception of eye abnormalities (see below), no individual event occurred in more than ≥10% subjects in either treatment group. The most common events were upper respiratory infection and injury. All other events occurred in <3% subjects in either treatment group.

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

CNS/Psychiatric Events

During the prophylactic phase, a total of 111/492 (22.6%) subjects in the tafenoquine group and 39/162 (24.1%) subjects in the mefloquine group reported CNS/psychiatric adverse events. The most common events in the tafenoquine and mefloquine groups respectively were headache (12.4%, 12.3%), vertigo (4.5%, 4.9%) and somnolence (2.4%, 3.7%). No other event occurred in >2% subjects in either treatment group and there were no marked differences in the incidence or nature of events between the treatment groups.

During the relapse follow-up phase, a total of 36/492 subjects (7.3%) in the tafenoquine group and 12/162 (7.4%) in the mefloquine group reported CNS/psychiatric adverse events. The nature of the adverse events was similar to those reported in the prophylactic phase and there were no notable difference between the treatment groups.

Serious Adverse Events and Withdrawals

A total of 23 subjects experienced serious adverse events during the prophylactic phase: 18/492 (3.7%) subjects in the tafenoquine group and 5/162 (3.1%) subjects in the mefloquine group. In addition, 10 subjects experienced serious adverse events during the relapse follow-up phase; 8/492 (1.6%) subjects in the tafenoquine/placebo group and 2/162 (1.2%) subjects in the mefloquine/primaquine group. In 7 subjects (all in the tafenoquine group) the serious adverse events had a suspected relationship to study treatment. These were 5 subjects with eye abnormalities and 2 subjects with gastrointestinal symptoms: 1 with abdominal pain and 1 with abdominal pain and diarrhoea. There were no deaths reported during the prophylactic phase or during relapse follow-up phase.

A total of 14 subjects withdrew during the prophylactic phase: 11/492 (2.2%) in the tafenoquine group and 3/162 (1.9%) in the mefloquine group. Most of the events leading to withdrawal were injuries or arthralgia, none of which was reported as related to study treatment. Three subjects, all in the tafenoquine group, had events reported with a suspected relationship to study treatment: abdominal pain, depression and hyperaesthesia.

Phospholipidosis Assessments

Ophthalmic Assessments: A total of 74 tafenoquine subjects and 21 mefloquine subject sunder went ophthalmic examination at baseline, including visual acuity and field tests, colour vision tests and physical examination. No subjects had an clinically significant abnormalities at baseline. At the end of prophylaxis visit, corneal deposits (vortex keratopathy) or suspected corneal deposits were reported in 69/74 (93.2%) of subjects in the tafenoquine group and 0/21 subjects in the mefloquine group. Due to this unexpected finding, more detailed examinations were carried out than had been planned in the protocol, including detailed retinal and corneal examination and photography. Some of

these examinations were conducted with the knowledge that the subject had corneal deposits and were therefore unblinded.

There were no notable changes from baseline or differences between the treatment groups in visual field tests (Amsler Grid and Humphrey Perimetry), visual acuity (Snellen) or colour vision (Ishihara, SPP2 plates, FM100 test).

Subjects with corneal deposits were followed up beyond the scheduled 3-month follow-up visit during the relapse follow-up period. Results are shown below:

	End of Prophylaxis	3 Months*	6 Months*	1 year*
No. of subjects with vortex keratopathy	69/74 (93.2%)	32/74 (43.2%)	6/74 (8.1%)	0
No. subjects with vortex keratopathy resolved		37/69 (53.6%)	63/69 (91.3%)	69/69 (100%)

* Timings are approximate

At each follow-up corneal deposits were noted to have improved, with all subjects having resolved within 1 year of stopping study medication.

Fundoscopy examination revealed abnormalities (e.g. granularity/pigmentation of retinal pigment epithelium, hard drusen) in 27/69 (39.1%) of tafenoquine subjects and 4/17 (23.5%) of mefloquine subjects. However it should be noted that the examiners were aware of corneal deposits (if present) while conducting this examination. Fundus fluoroscein angiograms (FFA) were performed in 14 tafenoquine subjects and 1 mefloquine subject in whom possible retinal findings had been observed; of these 4/14 (28.6%) subjects in the tafenoquine group and 1/1 (100%) subject in the mefloquine group were considered to have abnormal findings.

As a result of these findings, an expert ophthalmology board were asked to review the data from this study. They concluded that the corneal changes were benign, fully reversible and similar to those seen with other drugs, such as chloroquine. The expert ophthalmology advisory board advised that vision had not been affected in any of these subjects. Lack of baseline retinal photography data meant that the relevance of the retinal findings (observed on fundoscopy and fundus fluoroscein angiograms) could not be ascertained. They noted that the results observed could reflect normal variability and the subjective nature of the examinations. They did not consider that the FFA results provided evidence of a drug effect.

Lung Function tests: Diffusion capacity of the lungs to carbon monoxide (DLCO) and forced expiratory volume (FEV_1) was measured in 77 tafenoquine subjects and 21 mefloquine subjects. There were no differences between the treatment groups in the change in percent predicted DLCO or FEV_1 from baseline.

Electron microscopy of peripheral blood lymphocytes: no clinically significant changes in blood lymphocytes were observed in either treatment group.

Methemoglobin assessments: Methemoglobin was measured at baseline, at the end of the prophylactic phase and at the 3-month follow-up visit. At the end of the prophylactic phase, the mean increase from baseline in methaemoglobin was larger in the tafenoquine group (1.8%) than in the mefloquine group (0.1%). At the end of the 3 month follow-up, however, the increase from baseline was small and similar in both treatment groups (0.1-0.2%).

ECG Data

ECGs were performed at baseline and at end of the prophylactic phase in 77 tafenoquine subjects and 21 mefloquine subjects. In the tafenoquine group, mean QTc interval showed a small reduction (-4.5msec) from baseline whereas mean QTc interval showed a small increase (1.6msec) from baseline in the mefloquine group. These changes were not considered to be clinically relevant.

Laboratory Data

At the end of the prophylactic phase there were generally only small changes from baseline in laboratory test results and few marked differences between the treatment groups. The change from baseline at each visit (mean increase and number of subjects with a significant increase (F2)) in creatinine and bilirubin was slightly larger in the tafenoquine than in the mefloquine group. There was also a more noticeable decrease from baseline in hematocrit values in the tafenoquine group compared to the mefloquine group. Conversely, the increase from baseline in platelets at each visit was larger in the mefloquine than in the tafenoquine group.

Only a small number of subjects (~5) had haematology assessments performed at follow-up, so it is not possible to draw any conclusions from this data. The differences between the treatment groups for biochemistry parameters had mostly resolved at follow-up.

For all laboratory parameters, <5% of subjects in either group had post-treatment results flagged as clinically significant (F3).

Long-term renal follow-up: In total, there were 246 subjects with an increased serum creatinine concentration at end of prophylaxis and/or follow-up. Twenty-nine of these were subsequently been discharged from the ADF, though none for renally related medical conditions. In total, 186 subjects were contacted and 183 subjects consented to take part in the follow-up. Of these, 147 subjects were from the tafenoquine treatment group and 36 subjects were from the mefloquine treatment group. The demographics of this group were very similar to the overall study population.

A total of 173/183 (95%) subjects had normal renal function tests at their first or second follow-up visit; 140/147 (95.2%) subjects in the tafenoquine group and 30/33 (91.7%) subjects in the mefloquine group.

Overall, 10 subjects were referred for follow-up with a renal consultant for the reasons described below:

COMMERCIAL IN CONFIDENCE

	Treatment Group	
	Tafenoquine N=147	Mefloquine N=36
Referred for renal follow-up	7 (4.8%)	3 (8.3%)
Creatinine above upper limit of normal	0	1 (2.8%)
Creatinine ≥0.03mmol/L above baseline	2 (1.4%)	1 (2.8%)
Clinically significant urinalysis result	5 (3.4%)	2 (5.6%)

All 10 subjects were confirmed by the renal physician as having no signs of chronic renal damage. This follow-up did not demonstrate any evidence of long-term renal damage in healthy subjects who had received tafenoquine for 6 months.

Conclusions:

- Tafenoquine at a weekly dose of 200mg was well tolerated amongst subjects in a military deployment.
- The incidence and nature of adverse events was similar between the two treatment groups. The most common adverse events were gastroenteritis and injury.
- Tafenoquine was associated with the development of vortex keratopathy (linked to phospholipidosis) in 69/74 (93.2%) subjects tested (compared to no mefloquine subjects). This effect was benign and reversible, with resolution in >90% subjects at 6 months and complete resolution in all subject by 1 year post-treatment.
- No significant changes were seen in most laboratory parameters during the study. Increases in methemoglobin in the tafenoquine were small. Renal follow-up confirmed a lack of long-term renal effects of tafenoquine.
- Both tafenoquine and mefloquine were highly effective in preventing malaria, with no subjects developing parasitemia during the prophylactic phase. During the relapse follow-up phase, <1% of subjects in either treatment group developed *P.vivax* malaria.

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Lieutenant Colonel M. Edstein
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Dear LTCOL Edstein

AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE (ADHREC) PROTOCOL 216/00, 249/01 AND 328/03.

1. Thank you for providing the Committee with the support papers for the above protocol numbers. The papers were presented at the ADHREC meeting held on 15 Oct 07.

2. The Committee congratulates you on the completion of your projects and wishes you all the best for any research ventures you may undertake in the future.

3. Our file has now been finalised.

Yours sincerely

s22 [redacted]

Doctor Rosemary A. Laudy
Executive Secretary
Australian Defence Human Research Ethics Committee
CP2-7-130
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CANBERRA ACT 2600

22 October 2007

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Report

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Population Pharmacokinetics of Tafenoquine during Malaria Prophylaxis in Healthy Subjects[▽]

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The population pharmacokinetics of tafenoquine were studied in Australian soldiers taking tafenoquine for malaria prophylaxis. The subjects (476 males and 14 females) received a loading dose of 200 mg tafenoquine base daily for 3 days, followed by a weekly dose of 200 mg tafenoquine for 6 months. Blood samples were collected from each subject after the last loading dose and then at weeks 4, 8, and 16. Plasma tafenoquine concentrations were determined by liquid chromatography-tandem mass spectrometry. Population modeling was performed with NONMEM, using a one-compartment model. Typical values of the first-order absorption rate constant (K_a), clearance (CL/F), and volume of distribution (V/F) were 0.243 h^{-1}, 0.056 liters/h/kg, and 23.7 liters/kg, respectively. The intersubject variability (coefficient of variation) in CL/F and V/F was 18% and 22%, respectively. The interoccasion variability in CL/F was 18%, and the mean elimination half-life was 12.7 days. A positive linear association between weight and both CL/F and V/F was found, but this had insufficient impact to warrant dosage adjustments. Model robustness was assessed by a nonparametric bootstrap (200 samples). A degenerate visual predictive check indicated that the raw data mirrored the postdose concentration-time profiles simulated (n = 1,000) from the final model. Individual pharmacokinetic estimates for tafenoquine did not predict the prophylactic outcome with the drug for four subjects who relapsed with *Plasmodium vivax* malaria, as they had similar pharmacokinetics to those who were free of malaria infection. No obvious pattern existed between the plasma tafenoquine concentration and the pharmacokinetic parameter values for subjects with and without drug-associated moderate or severe adverse events. This validated population pharmacokinetic model satisfactorily describes the disposition and variability of tafenoquine used for long-term malaria prophylaxis in a large cohort of soldiers on military deployment.

Tafenoquine, a synthetic analog of primaquine, is a new 8-aminoquinoline antimalarial drug being codeveloped by GlaxoSmithKline Pharmaceuticals and the Walter Reed Army Institute of Research (1). Clinical trials have shown tafenoquine to be an effective antimalarial agent that has been generally well tolerated, with transient gastrointestinal discomfort being the most commonly reported adverse event (8, 10, 11, 13,). To date, it has been evaluated in more than 2,000 subjects in six phase II clinical studies. Since tafenoquine acts on all malaria stages, it has potential in the chemoprophylaxis of malaria, in radical cure/relapse prevention of *Plasmodium vivax* infections, and as a transmission-blocking agent (gametocytocidal activity).

The pharmacokinetics of tafenoquine in humans have been derived from studies after oral administration, as no parenteral formulation exists. Tafenoquine is slowly absorbed following oral administration, with maximum plasma concentrations observed at about 12-h postdose in fasted subjects (1). Plasma tafenoquine concentration-time data have been described by a one-compartment model with first-order absorption and elimination (1, 2). The elimination half-life of tafenoquine is about 2 weeks. It is extensively distributed to tissues, with a large volume of distribution and a low clearance, but data on the metabolism of tafenoquine in humans are limited. Although animal studies have shown that absorbed tafenoquine secreted via the bile is found predominantly in the form of metabolites, which accounted for the majority of the drug-related material eliminated in the urine and feces, unchanged tafenoquine was the only drug-related component detected in human plasma by high-performance liquid chromatography–mass spectrometry (HPLC-MS) and HPLC with fluorescence detection (GlaxoSmithKline Pharmaceuticals, unpublished data).

Tafenoquine is highly effective in preventing malaria infections following a weekly dose of either 200 mg or 400 mg for 13 weeks (13) or 400 mg monthly for 6 months (15). In developing the dosage regimen for malaria prophylaxis, a phase III study was conducted to assess the safety, tolerability, and effectiveness of tafenoquine in Australian soldiers deployed for 6 months on peacekeeping duties to an area where malaria is endemic. The full clinical results of that study will be published elsewhere. The soldiers were on a weekly regimen of 200 mg of tafenoquine, and blood samples were collected on four occasions for drug analysis. No malaria infections occurred during the prophylactic phase, but four soldiers were diagnosed with *P. vivax* infection after returning to Australia.

The primary aim of the present study was to use these data to develop a population pharmacokinetic model for tafenoquine and to estimate the disposition of this drug in the target population of soldiers on military deployment. Secondary aims

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Use of the Quinoline anti-malarial drugs Mefloquine and Tafenoquine in the Australian Defence Force
Submission 1 - Supplementary Submission 1

were to determine whether individual pharmacokinetic estimates for tafenoquine would predict prophylactic outcomes and to investigate if there was any relationship between tafenoquine concentrations and drug-associated adverse events.

MATERIALS AND METHODS

Study design and subjects. The clinical trial was designed as a prospective, randomized, double-blind comparative study of the safety, tolerability, and effectiveness of tafenoquine and mefloquine in Australian soldiers on weekly malaria prophylaxis. The subjects were deployed on peacekeeping duties to East Timor for 6 months. They all were judged to be healthy by a complete medical history, physical examination, and normal hematological and biochemical values. They had to be glucose-6-phosphate dehydrogenase normal and willing and able to give written informed consent and comply with the study protocol. Females were excluded if they were pregnant, lactating, or unwilling/unable to comply with recognized contraceptive methods. The study protocol received prior written approval by the Australian Defence Human Research Ethics Committee and the U.S. Army Human Subject Research Review Board.

Tafenoquine dosing regimen. Following a loading dose regimen of 200 mg tafenoquine base daily for three consecutive days, the subjects then received an oral weekly maintenance dose of 200 mg tafenoquine over approximately 6 months. An opaque Swedish Orange size 1 hard gelatin capsule (Capsugel) containing tafenoquine at 200 mg (pure free base) was used as the dosage form. Subjects were directed to take their *tafenoquine* with food (breakfast or dinner) at the same time each week. Dosage administration was observed and recorded for each subject.

Pharmacokinetic sampling. The sampling design was guided by the results from a previous smaller study of Thai soldiers (2) and also by logistical issues of the field operations. Blood samples were collected at prerandomized times after the last loading dose and then at prerandomized times at weeks 4, 8, and 16. Samples were collected on predetermined days after dosing on each of the assessment weeks. The predetermined days included day 1 (early postdose; absorption phase), days 3 and 5 (72 to 120 h postdose), and day 7 (predose; trough phase). For example, on week 4, one group of soldiers (about 125 subjects) was bled on day 1, one group was bled on day 3, one group was bled on day 5, and one group was bled on day 7. Thereafter, the groups of soldiers were bled in a cyclical fashion such that at the end of the study each group had been bled on at least one occasion on days 1, 3, 5, and 7. However, the sample for day 2 of the study (1 to 12 h; post-final loading dose) was collected from the study subjects.

Blood (7 ml) was drawn by venipuncture into EDTA tubes and transported on ice bricks to the field laboratory within 3 h of collection. Whole-blood samples were centrifuged at ~1,200 × *g* for 15 min (Sigma, Quantum, Australia), and plasmas were separated and stored in liquid nitrogen (<4 weeks) and then air freighted on dry ice to Quintiles Limited (Edinburgh, United Kingdom) for storage at −70°C until analysis. Tafenoquine was stable under these handling and storage conditions.

Measurement of tafenoquine. Plasma tafenoquine concentrations were determined using a validated HPLC method with a triple-quadrupole mass spectrometer. Briefly, plasma (0.05 ml) was spiked with [$^2H_4$,^{15}N]tafenoquine as a stable-isotope-labeled internal standard, and the protein was precipitated with methanol, followed by centrifugation and then injection of 4 μl of the supernatant fluid onto a reversed-phase HPLC column (4-μm-diameter particles; Genesis C_{18} column; 30 mm × 2.1-mm internal diameter) held at 40°C. The mobile phase was methanol-1 mM ammonium acetate buffer, pH 2.5 (70:30 [vol/vol]), pumped at 1 ml/min and split approximately 1 to 4 into the TurboIonSpray interface of a PE-Sciex API 3000 LC/MS/MS system (Applied Biosystems) operated in positive-ion multiple-reaction monitoring mode. A chromatographic cycle time of 1.3 min was used, with the peaks being eluted at 0.4 min. The multiple-reaction monitoring transitions monitored were 464 to 379 *m/z* for tafenoquine and 469 to 379 *m/z* for stable-isotope-labeled tafenoquine. Linear responses in analyte/internal standard peak area ratios were observed for tafenoquine concentrations ranging from 5 to 500 ng/ml, using a weighted ($1/C^2$) linear regression. Results of a three-run validation gave an intra-assay imprecision (coefficient of variation [CV%]) of <5.8% and an interassay imprecision of <7.3%, with an inaccuracy of 1.5 to 4.4%. The lower limit of quantification of the method was 5 ng/ml.

Population pharmacokinetic modeling. The population pharmacokinetics of tafenoquine were determined in double precision by using NONMEM (version 5, level 1.1; Globomax LLC, Hanover, MD) in conjunction with a G77 compiler. A one-compartment model with first-order absorption and elimination was fitted to the data, using first-order conditional estimation with *interaction*. An initial analysis was conducted by permitting NONMEM to estimate the base model parameters (i.e., no covariates). The influence of mean-centered continuous variables, i.e., age, current weight, and estimated creatinine clearance (CL_{CR} [by the Cockcroft-Gault method]), and the categorical variables, i.e., sex or evidence of phospholipidosis, was assessed by adding these to the base model in turn and noting the change in the objective function value (OFV). The inclusion of a covariate improved the fit of the data to the model if there was a decrease in the OFV. The difference between a pair of OFV values when a covariate was included (full model) and then excluded (reduced model) was tested for significance ($\alpha = 0.01$), using the chi-square statistic with 1 degree of freedom ($\chi^2_{1,0.01} = 6.6$).

The interindividual variability (IIV) was modeled, assuming a log-normal distribution, as follows:

$$CL/F_j = CL/F \cdot e^{(\eta_{j,CL/F} + \kappa_{j,CL/F})}$$

$$V/F_j = V/F \cdot e^{(\eta_{j,V/F} + \kappa_{j,V/F})}$$

$$K_{a_j} = K_a \cdot e^{(\eta_{j,K_a} + \kappa_{j,K_a})}$$

where CL/F_j, V/F_j, and K_{a_j} represent the true but unknown values of the parameters for the *j*th subject on the *j*th occasion about the typical respective population values CL/F, V/F, and K_a. The parameters $\eta_{j,CL/F}$, $\eta_{j,V/F}$, and η_{j,K_a} are random variables distributed with means of 0 and respective variances of $\omega^2_{CL/F}$, $\omega^2_{V/F}$, and $\omega^2_{K_a}$. K (kappa) is a random variable representing the variability of a given pharmacokinetic parameter value on different occasions, with an occasion being defined a priori as a dose or sequential doses followed by at least one observation (in this study, there were typically four occasions). The interoccasion variability (IOV) was assumed to be sampled from a normal distribution having a mean of 0 and a variance of π^2. In modeling the IOV, it was assumed that the variances of each parameter were sampled from the same distribution. The residual unexplained variability (RUV) among observed plasma tafenoquine concentrations and those predicted by the final population model were estimated by a combined proportional plus additive error model, as follows: $C_{ij} = C_{pred,ij}(1 + \varepsilon_{1,ij}) + \varepsilon_{2,ij}$, where C_{ij} is the *i*th observed concentration in the *j*th subject, $C_{pred,ij}$ is the plasma tafenoquine concentration predicted by the pharmacokinetic model, and $\varepsilon_{1,ij}$ and $\varepsilon_{2,ij}$ are randomly distributed variables having mean values of 0 and variances of σ_1^2 and σ_2^2, respectively.

Model assessment. The final model was assessed by an inspection of standard diagnostic plots of observed concentration versus population model predicted concentration and separate plots of weighted residual versus model-predicted concentration, elapsed time, subject identification, and screened covariates (3). A degenerate visual predictive check was performed by simulating from the final model 1,000 concentrations at each of 44 sampling times of up to 200 h postdose, at week 1 (after the third loading dose), and then at weeks 4, 8, and 16 during maintenance dosing. The 50th percentile concentration (as an estimator of the population-predicted concentration) and the 5th and 95th percentile concentrations were processed by ActivePerl (v.5.8.4; ActiveState) and then plotted against elapsed time for each of the above four sampling windows. Observed tafenoquine concentrations were superimposed on the plots. Model robustness was assessed by a nonparametric bootstrap, with replacement, of 200 NONMEM runs of the final model, comparing the bootstrapped median parameter values and the percentile bootstrap 90% confidence intervals (4, 5) with the respective values estimated in the final model.

Adverse events, severity rating, and association with drug. As part of the clinical phase III trial, adverse events were elicited by an investigator asking the subject a nonleading question, such as "Do you feel differently in any way since starting the new treatment?" A physician assessed the level of relationship of any adverse event on the basis of the subject's response and any temporal association and/or known adverse responses to the drug. The physician graded the severity of adverse events as follows: mild, not affecting daily activities; moderate, causing some interference with daily activities; severe, daily duties could not be completed. Attribution or relationship to tafenoquine was judged by the physician to be not related, unlikely to be related, suspected (reasonable probability) to be related, or probably related.

RESULTS

Population characteristics. The study population consisted of 476 males and 14 females, with a mean (± standard deviation [SD]) age of 25.4 ± 5.3 years (range, 18 to 47 years) and

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TABLE 1. Development of structural model for pharmacokinetics of tafenoquine

Model	Parameterization[a]	ΔOFV[a]
1	$CL/F = \theta_1$; $V/F = \theta_2$; $K_a = \theta_3$	
2	$CL/F = \theta_1 \cdot (1 + \theta_4 \cdot age/25.4)$; $V/F = \theta_2$; $K_a = \theta_3$	−2
3	$CL/F = \theta_1$; $V/F = \theta_2 \cdot (1 + \theta_4 \cdot age/25.4)$; $K_a = \theta_3$	−9[b]
4	$CL/F = \theta_1 \cdot (1 + \theta_4 \cdot CL_{CR}/121)$; $V/F = \theta_2$; $K_a = \theta_3$	−4
5	$CL/F = \theta_1 \cdot PHOS + \theta_4 \cdot (1 - PHOS)$; $V/F = \theta_2$; $K_a = \theta_3$	0
6	$CL/F = \theta_1$; $V/F = \theta_2 \cdot PHOS + \theta_4 \cdot (1 - PHOS)$; $K_a = \theta_3$	−1[b]
7	$CL/F = \theta_1 \cdot sex + \theta_4 \cdot (1 - sex)$; $V/F = \theta_2$; $K_a = \theta_3$	−3[b]
8	$CL/F = \theta_1$; $V/F = \theta_2 \cdot sex + \theta_4 \cdot (1 - sex)$; $K_a = \theta_3$	−12
9[c]	$CL/F = \theta_1 \cdot (1 + \theta_4 \cdot WT/80.9)$; $V/F = \theta_2 \cdot (1 + \theta_5 \cdot WT/80.9)$; $K_a = \theta_3$	−39
10	$CL/F = \theta_1 \cdot (WT/70)^{0.75}$; $V/F = \theta_2 \cdot (WT/70)^{1.0}$; $K_a = \theta_3$	+37[b]

[a] ΔOFV, change in OFV from that of model 1 (OFV = 22,177).
[b] Rounding errors occurred during fitting.
[c] Final model.
[d] WT/80.9, body weight (kg) centered on average weight (80.9 kg); age/25.4, age (years) centered on average age (25.4 years); $CL_{CR}/121$, CL_{CR} (ml/min) centered on average CL_{CR} (121 ml/min); PHOS, phospholipidosis (tested in 77 subjects; 1 = phospholipidosis present, 0 = phospholipidosis not present); sex, male = 0 and female = 1.

mean (± SD) weight of 80.9 ± 11.9 kg (range, 50 to 135 kg). ...d but eight were of Caucasian background. Of the 490 subjects, 2 subjects provided one blood sample, 3 subjects provided two blood samples, 23 subjects provided three blood samples, and the remaining 462 subjects provided four blood samples, giving a total of 1,925 plasma concentration-time points available for the pharmacokinetic analyses.

Population pharmacokinetic modeling. Summary results of the population model-building process are shown in Table 1. The data did not support the inclusion of an absorption lag time in any model. Neither age nor CL_{CR} on *CL/F* significantly improved the fit, nor did sex or phospholipidosis as indicator variables. Both age and sex effects on *V/F* produced small but significant decreases in the OFV, of 9 and 12, respectively. Use of an allometric size model scaled to 70 kg for *CL/F* (power, 0.75) and *V/F* (power, 1.0) was not supported (OFV = +37). Inclusion of centered linear weight on both *CL/F* and *V/F* significantly decreased the OFV, from 22,177 to 22,138. This model predicted that a 1-kg change in weight from the population average value of 80.9 kg would give a commensurate change of 0.0167 liters/h (0.38%) in *CL/F* and a change of 9.7 liters (0.51%) in *V/F*. The linear, positive influence of weight on both *CL/F* and *V/F* is shown in Fig. 1a and b, respectively.

Modeling the covariance between $\omega^2_{CL/F}$ and $\omega^2_{V/F}$ reduced the OFV from 22,265 to 22,248 compared with the corresponding model when $\omega^2_{CL/F}$ and $\omega^2_{V/F}$ were assumed to be independent. Inclusion of the IOV for *CL/F* reduced the OFV further, to 22,177. However, while the addition of IOV to *V/F* further reduced the OFV, the value for $\omega^2_{V/F}$ was suspiciously low and the correlation coefficient (r) calculated from the diagonal and off-diagonal elements of the variance matrix [$r = \omega^2_{CL/F,V/F}/(\omega^2_{CL/F} \cdot \omega^2_{CL/F})^{0.5}$] was ~1, indicating an inappropriate variance model. The RUV was best modeled by using a combined proportional and additive model, as seen by an increase in the OFV and by numerical difficulties when the additive and proportional models were used separately.

Parameter values for the final population model and the bootstrap validation are shown in Table 2. The estimated time (T_{max}) for peak concentration to occur after a dose was 21.4 ± 8.57 h, calculated from each subject's conditional estimates of K_a and K_e by the standard formula $T_{max} = \ln(K_a/K_e)/(K_a - K_e)$ for a one-compartment extravascular model. The observed mean (± SD) peak tafenoquine concentration measured in samples drawn within 5% of the time of the estimated mean population T_{max} (21.4 h) for 42 subjects at weeks 4, 8, and 16 was 321 ± 63 ng/ml. The observed mean (± SD) trough tafenoquine concentration drawn within 5% of the target 168-h-postdose sampling time for 162 subjects at weeks 4, 8, and 16 was 221 ± 57 ng/ml. The typical population *CL/F* and *V/F*

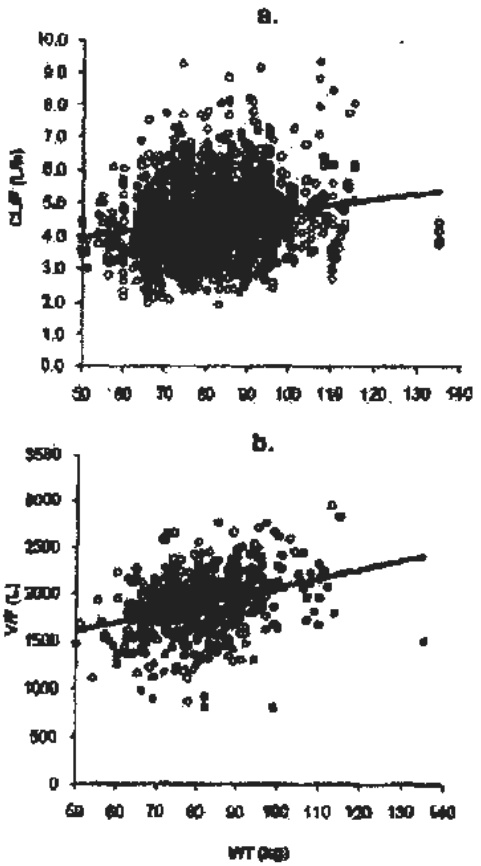

FIG. 1. Relationship of body weight (WT) to individual estimates of (a) *CL/F* and (b) *V/F* for tafenoquine.

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TABLE 2. Comparison of parameter estimates for the population model with the results of 200 bootstrapped runs

Parameter and model	Final model value	Bootstrap value (n = 200) (median [90% CI])[b]
Structural model[a]		
CL/F (θ_1; liters/h)	3.02	3.01 (2.42–3.52)
V/F (θ_2; liters)	1,110	1,110 (674–1,382)
K_a (θ_3; h^{-1})	0.243	0.245 (0.213–0.280)
Weight centered on CL/F[c]	0.448	0.447 (0.249–0.816)
Weight centered on V/F[d]	0.713	0.713 (0.371–1.20)
Variance model		
$IIV_{CL/F}$ (CV%)	18	18 (16–20)
$IIV_{V/F}$ (CV%)	22	22 (20–25)
IIV_{K_a} (CV%)	76	75 (64–85)
$IOV_{CL/F}$ (CV%)	18	18 (16–20)
RUV (CV%)	5.9	5.9 (4.7–7.4)
RUV (ng/ml)	22.9	23.1 (18.7–26.3)

[a] $CL/F = \theta_1 \cdot (1 + \theta_4 \cdot WT/80.9)$; $V/F = \theta_2 \cdot (1 + \theta_5 \cdot WT/80.9)$; $K_a = \theta_3$.
[b] Percentile bootstrap 90% confidence interval (5th to 95th percentiles).
[c] Linear coefficient (θ_4) for weight centered on CL/F.
[d] Linear coefficient (θ_5) for weight centered on V/F.

values for all subjects, with a mean weight of 80.9 kg, were 4.37 liters/h and 1,901 liters, respectively. The typical value of K_a over all subjects was 0.243 h^{-1}. The IIV about CL/F, V/F, and K_a was 18%, 22%, and 76%, respectively. The IOV for CL/F was 18%. Mean values per kg for CL/F and V/F calculated from conditional estimates for each subject were 0.056 ± 0.013 liters/h/kg and 23.7 ± 4.5 liters/kg, respectively. The elimination half-life ($t_{1/2}$), derived from the expression $t_{1/2} = (0.693 \cdot V/F)/(CL/F)$ with individual estimates of CL/F and V/F, was 12.7 ± 3.0 days.

Routine diagnostic weighted residuals versus population model-predicted values (data not shown) were symmetrically distributed and were mostly within about 3 units of the null ordinate, indicating a good fit of the model to the data. Plots of weighted residuals versus both subject identification and time (data not shown) were distributed symmetrically in a band with no obvious trend and were mostly within approximately 3 units of the null ordinate, indicating that no time-related factor affected the data and that no subject's data contributed to any marked deviation from the model. The bootstrapped median parameter values very closely agreed with the respective values from the final population model (Table 2). The degenerate visual predictive check showed the observed data to be symmetrically distributed about the 50th percentile profile, with approximately 10% of the data distributed outside the 5th- to 95th-percentile boundaries (Fig. 2a, b, c, and d).

Individual pharmacokinetics of tafenoquine in subjects with malaria and with drug-associated adverse events. The four subjects who had a relapse after returning to Australia had a mean (± SD) CL/F of 0.060 ± 0.014 liters/h/kg, a V/F of 23.2 ± 8.0 liters/kg, and a $t_{1/2}$ of 11.1 ± 2.3 days, calculated from conditional parameter estimates for each individual.

One or more adverse events with a suspected/probable relationship to tafenoquine were reported by 73 subjects. These were ranked as mild in 67 subjects (91.8%), moderate in 5 subjects (6.8%), and severe in 1 subject (1.4%) and encompassed the following: nausea, abdominal pain, flatulence, vomiting, vertigo, agitation, amnesia, headache, eye abnormality, reflux, dreaming abnormality, insomnia, somnolence, diarrhea, hyperesthesia, tremor, paranoia, headache, anorexia, depression, coordination abnormality, appetite increase, and thirst. Tafenoquine was not withdrawn in any of the 67 mild cases, but it was withdrawn for three subjects who reported either moderate hyperesthesia, abdominal pain, or depression. Assessment for phospholipidosis was carried out in a subgroup of 77 subjects because tafenoquine has cationic amphiphilic characteristics and, therefore, the potential to cause phospholipid accumulation. Table 3 shows adverse events reported in the five moderate cases and one severe case where tafenoquine was suspected to cause the discomfort, together with individual estimates of the pharmacokinetic responses for these subjects. All moderate adverse events were experienced 1 to 24 days after the initiation of tafenoquine, while the single subject with

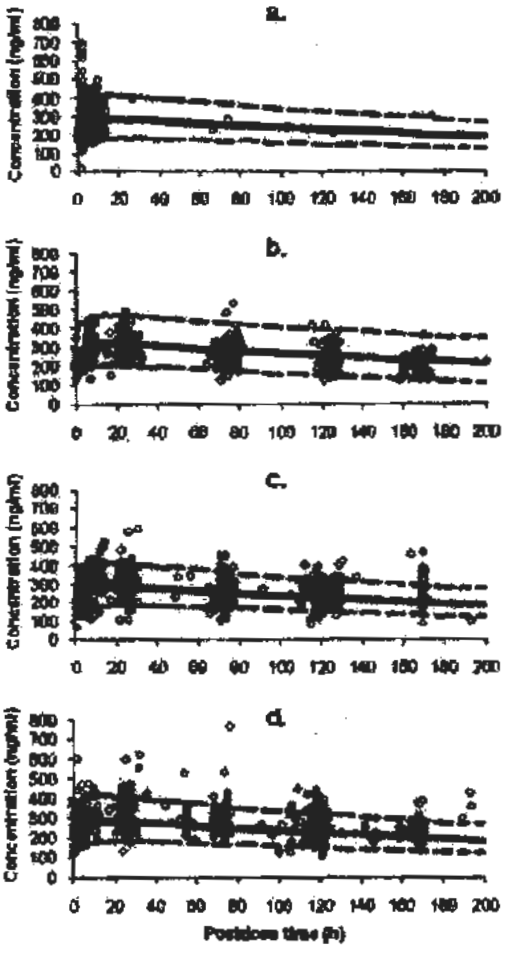

FIG. 2. Degenerate visual predictive check of the final population model for tafenoquine. Plots are shown for plasma tafenoquine concentration versus postdose time in sampling windows of (a) week 1 (post-loading dose), (b) week 4, (c) week 8, and (d) week 16. The population-predicted profile (50th percentile) is shown by the solid line, and the 90% prediction intervals estimated from 1,000 simulated concentrations over 200 h (postdose) are encompassed by the broken lines in each plot.

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TABLE 3. Tafenoquine pharmacokinetic data for six subjects reporting at least one adverse effect classified as severe (n = 1) or moderate (n = 5)

Adverse event	Treatment duration (days)[a]	Cumulative dose (mg)[b]	Dosing stopped	C_{max} (ng/ml)[c]	CL/F (liters/h/kg)	V/F (liters/kg)	$t_{1/2}$ (days)
Severe event							
Diarrhea and/or abdominal pain	2	400	No	*	0.059	24.4	12.0
Moderate events							
Insomnia	1	200	No	*	0.059	23.2	11.3
Hyperesthesia	12	800	Yes	283	0.046	20.7	13.1
Abdominal pain	20	1,000	Yes	253	0.053	27.8	15.1
Depression	24	1,000	Yes	275	0.061	25.1	12.0
Vomiting and/or nausea	3	600	No	315	0.077	26.1	9.8

[a] Number of days from starting dosing until adverse event reported.
[b] Total amount of drug taken before adverse event reported.
[c] Last plasma tafenoquine concentration before adverse event reported. *, adverse event was reported before first plasma sample was drawn.

were effects reported diarrhea and abdominal pain 2 days after commencing tafenoquine treatment.

DISCUSSION

This study of the population pharmacokinetics of tafenoquine in 490 Australian soldiers is the largest undertaken by far with this promising new oral antimalarial agent. Previously, a two-stage dose-ranging pharmacokinetic study was performed with 48 healthy adult males (Caucasian [n = 20], African-American [n = 12], and Hispanic [n = 16]) (1), while a subsequent population pharmacokinetic study was reported for 104 Thai soldiers on a monthly prophylactic regimen of tafenoquine (2). The present findings confirm the knowledge of tafenoquine disposition in humans and considerably extend the pharmacokinetic data to a large population of healthy, Caucasian military personnel deployed in field operations.

The apparent V/F was similar to that reported by Edstein et al. (2), but the systemic CL/F was greater (4.37 liters/h versus 3.20 liters/h). The derived typical elimination $t_{1/2}$ of 12.7 days was slightly shorter than the 14 to 16 days reported previously, which may partly reflect the fact that the last samples were drawn at only up to 1 week postdose and therefore the presumed "terminal" phase may have included some components of a distribution phase, but not substantial enough to be supported by a two-compartment model. The mean values for CL/F and V/F obtained by Brueckner et al. (1) for fasted subjects of similar average weight to that from this study were 5.7 liters/h and 2,558 liters, respectively, which are 30% to 35% higher than the present typical values. However, in the current study, the subjects took tafenoquine with food, which reportedly can increase the bioavailability (F) by up to one-third (R. P. Brueckner, personal communication), which brings the respective CL/F and V/F values into closer agreement when corrected for F. While the extent of tafenoquine absorption may be greater, food could also slow the rate of drug absorption, as evidenced by the typical K_a of 0.243 h^{-1}, compared with 0.391 h^{-1} and 0.694 h^{-1} reported by Brueckner et al. (1) and Edstein et al. (2), respectively. As a result, the average T_{max} of 21.4 h was greater than the 8.6 h to 13.8 h reported previously (1, 2), which as well as the influence of food, may reflect continuous absorption along the intestinal tract, perhaps due in part to microprecipitation and redissolution of tafenoquine, which is only slightly water soluble (1). Unpublished data on file (GlaxoSmithKline) for healthy volunteers showed mean (CV%) T_{max} values of 18.6 h (84%) and 26.3 h (126%) under fasted conditions and when administered with a standard high-fat meal, respectively, indicating that the T_{max} and its variability were increased by food. Nonetheless, it should be remembered that T_{max} is a model-dependent parameter in that the true value is likely to be overestimated when a one-compartment model is used compared with that for a two-compartment model. In agreement with previous reports (1, 2), there was marked IIV in the T_{max}, reflecting the considerable variability in both K_a and K_e, with the latter being estimated from conditional estimates of V/F and CL/F for each subject.

The variability in CL/F and V/F was not excessive, at 18% to 22%, most likely reflecting the uniformity of the military subjects. The variance model supported estimation of the IOV in CL/F but not that in V/F or K_a. While Edstein et al. (2) used a proportional (exponential) model for RUV, presently a combined additive-proportional RUV model was supported, which is the preferred model wherever possible, especially where the range of concentration data is as wide as in this study. There was a positive linear association between weight and both CL/F and V/F, but attempts to model these parameters using an allometric size model scaled to 70 kg were not supported by the data, most likely because of the reasonably narrow range of body weights. Although heavier subjects tended to have a slightly greater CL/F and V/F, this would not have any major implications for changes in the way that tafenoquine would be prescribed, at least on the basis of the pharmacokinetic data alone. Using the present steady-state plasma tafenoquine concentrations as the appropriate clinical target, a 20-kg change in weight would require changes in the loading dose and maintenance dose of only about 10% and 7.5%, respectively. Unpublished data (GlaxoSmithKline) indicated that a considerable fraction of a tafenoquine dose may be excreted unchanged, while the clinical data from the trial of which the present study was a part showed that mean serum creatinine concentrations increased 12.1 mmol/liter from baseline until the end of the prophylaxis. However, estimated creatinine clearance explained an insignificant amount of the variability

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about CL/F. Age explained a small yet significant amount of the variability in both *V/F* and CL/F but was positively correlated with weight and thus was not considered further.

In assessing performance, model robustness was evaluated via a nonparametric bootstrap, which indicated that randomly selected combinations of data gave very similar results to those obtained with the original data set. In addition, a degenerate visual predictive check showed that the raw data obtained after the third split loading dose and at week 4, 8, and 16 during maintenance dosing mirrored the corresponding profiles obtained from simulations using point estimates of the final model parameter values. This convenient approach has been shown elsewhere (16) to give a good approximation of the full posterior predictive check, in which the simulations are performed using posterior distributions of the parameter values (6), which are difficult to calculate from the NONMEM output. The predictive check showed, firstly, that the structural model was satisfactory by the symmetrical distribution of the ...y data about the 50th percentile profile and, secondly, that ...e variance model was appropriate, with about 10% of the raw data lying outside the 5th and 95th percentiles.

The prophylactic efficacy of tafenoquine is determined by its ability to prevent parasitemia from developing, which is associated with the susceptibility of malaria parasites to tafenoquine concentrations achieved in the target population. Tafenoquine has both causal prophylactic activity against the hepatic stages of the parasite and suppressive activity, which eradicates the erythrocytic stages of the parasite (1). In the present study, no subject developed parasitemia during the 6 months of prophylaxis, but four had a relapse of *P. vivax* infection after returning to Australia. In contrast, one subject in a population of 104 Thai soldiers on 400 mg tafenoquine monthly for 6 months developed vivax malaria during prophylaxis (15). At the time of diagnosis, the Thai soldier had a plasma tafenoquine concentration of 40 ng/ml, which was >5-fold lower than the mean steady-state trough tafenoquine concentration of 221 ng/ml presently recorded. Six Australian soldiers had tafenoquine concentrations of <100 ng/ml at either week 4, 8, or 16. Of those, only one subject had consistently ...wer tafenoquine concentrations (<120 ng/ml) on the three ...ccasions sampled and therefore may have had a reduced margin of suppressive protection against malaria infection. The Thai soldier who developed parasitemia also had consistently lower tafenoquine concentrations during the prophylactic phase (15). Unlike the Thai soldier, the four Australian soldiers who relapsed had comparable tafenoquine concentrations to subjects who did not have a recurrence of malaria. Although the number of subjects who relapsed was small, the individual estimates of the pharmacokinetic responses for these subjects did not provide a prediction or correlation with tafenoquine's prophylactic efficacy.

There was no apparent correlation between either the pharmacokinetic parameter values predicted for individual subjects or the last tafenoquine concentration measured in subjects reporting moderate or severe adverse events. These findings suggested that plasma tafenoquine concentrations are not the primary predictor of tafenoquine tolerability. This lack of an association between plasma drug concentrations and adverse events has also been seen with another antimalarial agent, mefloquine, which shares similar pharmacokinetic properties with tafenoquine (12) in that both are lipophilic, are slowly absorbed from the gastrointestinal tract, are extensively bound to tissues, and have elimination $t_{1/2}$ values of about 2 weeks (1, 2, 9, 14).

In conclusion, the pharmacokinetic properties of tafenoquine determined in this study support a weekly dosing regimen for prolonged periods. Although body weight influenced CL/F and *V/F*, it was not considered to have sufficient impact to warrant changing the maintenance or loading dose for any individual from such a population. Nonetheless, dose changes may be warranted for other patients who are markedly overweight or underweight compared with this homogenous group of soldiers. Any dosing requirements for markedly overweight subjects may need special consideration, as reviewed recently (7). Tafenoquine was generally well tolerated. Individual pharmacokinetic parameter estimates for subjects with malaria did not predict prophylactic outcomes, and plasma concentrations at steady state did not appear to be related to the occurrence of adverse events. Since this population was a homogenous group of healthy Australian soldiers of predominantly Caucasian background, additional pharmacokinetic studies may be required for other populations.

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The opinions expressed are those of the authors and do not necessarily reflect those of the Australian Defence Health Service or any extant Australian Defence Force policy.

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12 April 2010

(3) ITEM EIGHT – FINAL REPORTS

216-00 A randomized, double – blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-imune Australian soldiers deployed to East Timor.

Scientific article published in "Antimicrobial Agents and Chemotherapy" Feb 2010. ✓

Decision: Noted with thanks.
Action:
Executive

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Randomized, Double-Blind Study of the Safety, Tolerability, and Efficacy of Tafenoquine versus Mefloquine for Malaria Prophylaxis in Nonimmune Subjects[▽]

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This study represents the first phase III trial of the safety, tolerability, and effectiveness of tafenoquine for malaria prophylaxis. In a randomized (3:1), double-blinded study, Australian soldiers received weekly malaria prophylaxis with 200 mg tafenoquine (492 subjects) or 250 mg mefloquine (162 subjects) for 6 months on a peacekeeping deployment to East Timor. After returning to Australia, tafenoquine-receiving subjects received a placebo and mefloquine-receiving subjects received 30 mg primaquine daily for 14 days. There were no clinically significant differences between hematological and biochemical parameters of the treatment groups. Treatment-related adverse events for the two groups were similar (tafenoquine, 13.4%; mefloquine, 11.7%). Three subjects on tafenoquine (0.6%) and none on mefloquine discontinued prophylaxis because of possible drug-related adverse events. No diagnoses of malaria occurred for either group during deployment, but 4 cases (0.9%) and 1 case (0.7%) of *Plasmodium vivax* infection occurred among the tafenoquine and mefloquine groups, respectively, up to 20 weeks after discontinuation of medication. In a subset of subjects recruited for detailed safety assessments, treatment-related mild vortex keratopathy was detected in 93% (69 of 74) of tafenoquine subjects but none of the 21 mefloquine subjects. The vortex keratopathy was not associated with any effect on visual acuity and was fully resolved in all subjects by 1 year. Tafenoquine appears to be safe and well tolerated as malaria prophylaxis. Although the volunteers' precise exposure to malaria could not be proven in this study, tafenoquine appears to be a highly efficacious drug for malaria prophylaxis.

The continuing spread of multidrug-resistant *Plasmodium* species and concerns about adverse effects associated with antimalarial drugs has made the prevention of malaria problematic for nonimmune subjects, such as tourists and soldiers who travel to malaria endemic areas. No antimalarial drug is completely effective in preventing malaria (10); however, an ideal prophylactic drug would be highly effective against all malaria-inducing species, very well tolerated, and taken infrequently to enhance compliance (21). Currently, mefloquine, doxycycline, and atovaquone-proguanil are recommended for malaria prophylaxis (5, 23). These drugs are highly effective in preventing malaria but have shortcomings that limit their effectiveness, such as adverse effects, expense, and the difficulty of monitoring daily compliance within deployed military populations. Furthermore, none of these recommended drugs prevents the development and relapse of *Plasmodium vivax* and *P. ovale* dormant liver stages (hypnozoites).

Tafenoquine, a long-acting 8-aminoquinoline, is currently being codeveloped by GlaxoSmithKline (GSK) Research & Development Limited and the Walter Reed Army Institute of Research as a replacement for primaquine and for the prevention of malaria. Like primaquine, tafenoquine produces hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient recipients (21). Tafenoquine acts on all stages of the malaria parasite, with the potential to protect against all species of malaria parasites. Previous studies with a challenge model (4) and of indigenous populations in areas in which malaria is endemic have shown that tafenoquine was highly efficacious in preventing *P. falciparum* malaria and well tolerated (9, 13, 21). Tafenoquine was also shown to be efficacious in preventing both *P. falciparum* and *P. vivax* malaria for up to 6 months in Thai soldiers (22).

This first phase III study of tafenoquine for malaria prophylaxis was a randomized, double-blind, active controlled study carried out with healthy Australian soldiers deployed to East Timor as part of a United Nations (UN) peacekeeping mission. The primary study objective was to compare the safety and tolerability of tafenoquine with those of mefloquine in malaria prophylaxis for 6 months. A subset of 98 subjects underwent extra safety assessments to investigate the possible effects of phospholipidosis, methemoglobin, and cardiac safety. Since a

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Use of the Quinoline anti-malarial drugs Mefloquine and Tafenoquine in the Australian Defence Force
Submission 1 - Supplementary Submission 1

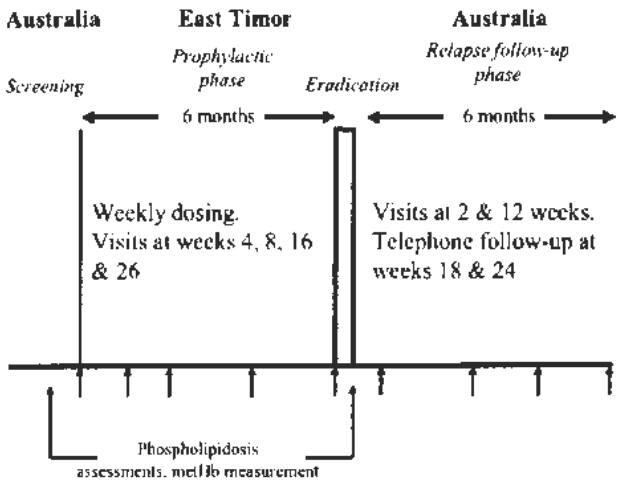

FIG. 1. Drug administration and safety analysis schedule for tafenoquine and mefloquine. metHb, methemoglobin.

placebo arm to document exposure was not possible, the key secondary objective was to assess the efficacy of tafenoquine in preventing *P. falciparum* and *P. vivax* malaria during and following deployment.

(This study was presented in part at the 51st Annual Meeting of the American Society of Tropical Medicine and Hygiene, Denver, CO, November 2002.)

MATERIALS AND METHODS

Study site and subjects. The subjects were Australian soldiers deployed on UN peacekeeping duties to East Timor from October 2000 to April 2001. The soldiers were deployed to the Bobonaro District, on the western border of East Timor. The study included male and female subjects who were between 18 and 55 years of age, judged to be healthy by a medical history and physical examination with normal hematological and biochemical values, G6PD normal, and willing and able to give written informed consent and comply with the study protocol. Females were excluded if they were pregnant, lactating, or unwilling/unable to comply with recognized contraceptive methods. Subjects with a history of psychiatric disorders and/or seizures were also excluded. All subjects gave written informed consent, and the study protocol was approved by the Australian Defence Human Research Ethics Committee (ADFHREC protocol no. 216/00) and the U.S. Army Human Subject Research Review Board.

Study design and drug administration. This comparative, randomized, double-blind, active controlled study had 4 phases: screening, loading, prophylactic phase, and relapse follow-up (Fig. 1). Following a loading-dose regimen of 200 mg tafenoquine or 250 mg mefloquine daily for 3 consecutive days, the subjects then received an oral weekly maintenance dose of 200 mg tafenoquine or 250 mg mefloquine for 26 ± 4 weeks, respectively. Subjects were directed to take their study medication at the same time each week with food (breakfast/dinner) to enhance drug bioavailability. Upon their return to Australia, subjects commenced a hypnozoite eradication regimen, receiving primaquine 15 mg twice a day (for the mefloquine group) or matched placebo twice a day (for the tafenoquine group) for 14 days. Drug compliance was observed and recorded for each subject by using medication logs.

Randomization. A coding memo block randomization system (block size = 8) to provide a 3:1 ratio of tafenoquine-receiving subjects to mefloquine-receiving subjects was used to assign the subjects to a treatment group. Study drugs were prepackaged and prelabeled with a unique study number.

Drug sources. Tafenoquine was supplied by GlaxoSmithKline in an opaque, hard gelatin capsule (Capsugel), each containing a 200-mg tafenoquine base. Placebo tafenoquine capsules were of identical appearance. Mefloquine (Lariam; 250-mg base tablet) was obtained from Hoffman-La Roche, and primaquine (15-mg base tablet) was supplied by GlaxoSmithKline. The matched placebos for mefloquine and primaquine were identical in external appearance to active capsules. All medication was provided in blinded individual foil blister packs and stored between 15°C to 30°C.

Safety and tolerability. Assessment of adverse events and sample collection for hematological and blood chemistry parameters were carried out at the loading stage and then at weeks 4, 8, 16, and 26 during the prophylactic phase and at weeks 2 and 12 during the relapse follow-up phase. Adverse event monitoring was supplemented by review of subjects' medical records. For a subset of 98 subjects (77 on tafenoquine and 21 on mefloquine), more-detailed safety assessments were performed. These subjects were assessed for phospholipidosis and its effects (by ophthalmic assessments, lung function tests, and electron microscopy of peripheral blood lymphocytes) and methemoglobin assessment and an electrocardiogram were performed (to assess QT interval) at screening and at the end of the prophylactic phase. Following the identification of corneal deposits at the end of this study, a wider range of ophthalmic assessments was included at follow-up.

Disclosure of adverse events was elicited by the investigator asking the subject the nonleading question, "Do you feel differently in any way since starting the new treatment?" A study physician assessed the level of relationship of any adverse event on the basis of the subject's response and any temporal association and/or known adverse responses to the drug. The physician graded the severity of adverse events as mild (not affecting daily activities), moderate (with some interference in daily activities), and severe (when daily duties could not be completed). A causal relationship to the study drug was judged by the physician to be not related, unlikely, suspected, or probable.

Efficacy assessment. Thick and thin blood smears were collected from all subjects at screening, at weeks 4, 8, 16, and 26 during the prophylactic phase, and at weeks 2 and 12 during the relapse follow-up phase or if symptoms suggestive of malaria developed. Telephone interviews with all subjects were carried out at weeks 18 and 24 during the relapse follow-up phase to determine their general health status. The Giemsa stain-treated blood smears were each read twice for malaria parasites by blinded microscopists at 2 separate institutions. A blood slide was considered negative if an examination of 200 oil immersion thick fields (magnification, ×1,000) showed no parasites. Any discrepant findings were to have been read by a third blinded expert microscopist and were to be used to define a prophylaxis failure if symptoms consistent with malaria were present.

Statistical analysis. With at least 450 subjects on tafenoquine and 150 subjects on mefloquine, the study had 94% power to detect a 10% difference in failure rates, assuming an underlying failure rate of 10% in each treatment group (15). Safety and tolerability analyses were performed on data from all subjects who took at least one dose of prophylactic study medication (tafenoquine or mefloquine). Hematological/blood chemistry values for the two groups were compared by a paired Student's *t* test, and 95% confidence intervals (CIs) were calculated. The efficacy analysis was performed for the per-protocol population, which was defined as the subjects who met the inclusion criteria, were protocol compliant, and completed the prophylactic and relapse follow-up phases. Proportions were examined by using a χ^2 test with Yates' correction or by Fisher's exact test. No adjustment was made for multiple testing.

RESULTS

Subject population. In total, 663 subjects were screened, and of these, 9 subjects failed the inclusion criteria. Of the remaining eligible subjects, 492 subjects were randomized to receive tafenoquine, and 162 subjects were randomized to receive mefloquine. Thirty-nine subjects (30 [6.1%] of the 492 tafenoquine subjects and 9 [5.6%] of the 162 mefloquine subjects) violated the protocol or did not complete the study, due to adverse events or other withdrawal reasons (Fig. 2). There were no marked differences between the groups in the proportions of subjects with protocol violations or withdrawals from the study (data not shown). The treatment groups were well balanced with respect to baseline demographic characteristics and history of malaria (Table 1), with the majority of subjects being white, male, and <35 years of age.

Compliance. As a result of observed therapy, compliance was high in both treatment groups (100% for the loading dose, 99% for the weekly regimens, and 96% for the follow-up antihypnozoite regimen).

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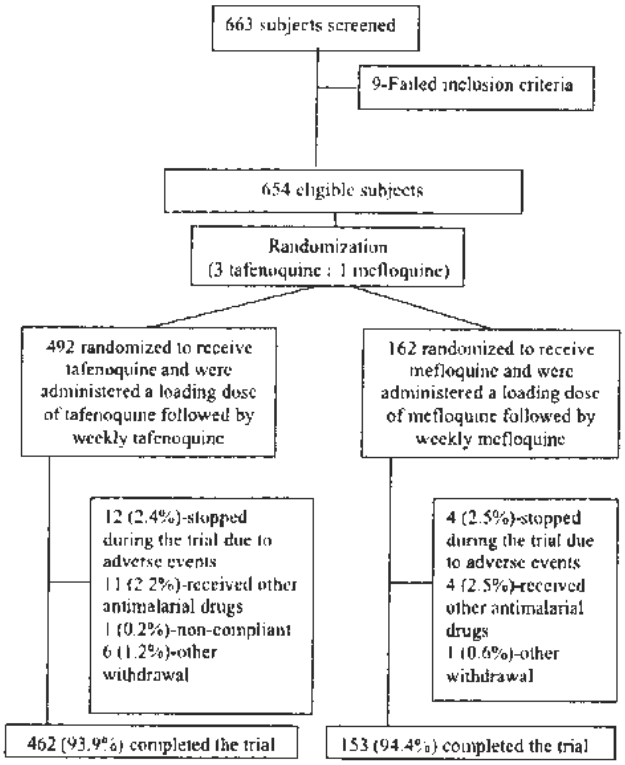

FIG. 2. Flow diagram of subject accountability during the study.

Routine laboratory tests. For most laboratory variables, the proportion of subjects with results that fell outside an extended normal range during the prophylactic phase was <5% (data not shown). In addition, the proportions of subjects with clinically significant changes from baseline values were similar across the treatment groups for most laboratory parameters. The parameters that were exceptions were hematocrit, bilirubin, and creatinine.

Decreases in hematocrits were seen in both subjects on tafenoquine and subjects on mefloquine, with up to 98 (20%) of the 492 tafenoquine subjects having a 15% decrease from the baseline at any one visit, compared to 23 (14.4%) of the 162 mefloquine subjects. However, only 2 subjects, both on tafenoquine, had a clinically significant hematocrit value (<85% of the lower limit of normal range) during the study. A higher proportion of tafenoquine subjects was reported to have an increase in bilirubin (>2 μmol/liter from the baseline) at any one visit during the study (10% of tafenoquine subjects versus 3.2% of mefloquine subjects). Of these, only 13 (2.6%) tafennquine subjects and 1 (0.6%) mefloquine subject had a clinically significant bilirubin value (>150% of the upper limit of normal range) at some point during the study. Serum creatinine increases (>125% baseline value) were seen in both the tafenoquine and mefloquine groups, with an increase in serum creatinine in up to 19% of tafenoquine subjects at any one visit versus 10% of mefloquine subjects. At the follow-up, 6 to 8% of subjects in both groups had creatinine values that were still 25% above the baseline; however, few subjects had values outside the normal range, and none of these values was considered clinically significant.

TABLE 1. Baseline demographic characteristics and previous malarial histories of subjects on tafenoquine and mefloquine for malaria prophylaxis

Characteristic	Value for subjects who received:	
	Tafenoquine (n = 492)	Mefloquine (n = 162)
No. (%) of subjects		
Gender		
Male	478 (97.2)	154 (95.1)
Female	14 (2.8)	8 (4.9)
Age (yr)		
18–25	286 (58.1)	97 (59.9)
26–35	178 (36.2)	48 (29.6)
36–45	27 (5.5)	16 (9.9)
46–55	1 (0.2)	1 (0.6)
Race		
White	484 (98.4)	160 (98.8)
Aboriginal/Torres Strait Islander	4 (0.8)	1 (0.6)
Other	4 (0.8)	1 (0.6)
Previous history of malaria	15 (3.0)	4 (2.5)
Having malaria attacks in 6 mo prior to deployment	9 (1.8)	1 (0.6)
Age		
Mean (SD)	25.4 (5.3)	26.0 (6.5)
Range	18–47	18–51
Weight (kg)		
Mean (SD)	80.9 (11.9)	81.3 (12.2)
Range	50–135	53–135
Height (cm)		
Mean (SD)	177.8 (7.0)	177.1 (6.7)
Range	155–198	157–192

Safety evaluation subgroup. The ophthalmic assessments in the subgroup of subjects on tafenoquine and mefloquine are summarized in Table 2. At the end of prophylaxis, vortex keratopathy (corneal deposits) was found in 69 (93.2%) of 74

TABLE 2. Ophthalmic assessments of a subgroup of subjects on tafenoquine or mefloquine

Activity	Screening	Posttreatment assessment
Visual field tests	Amsler grid	Amsler grid Humphrey perimetry
Visual acuity	Snellen chart	Snellen chart
Color vision	Ishihara test	Ishihara test Standard pseudoisochromatic plates part 2 Farnsworth-Munsell 100 hue test
Physical examination	Fundoscopy Corneal examination	Fundoscopy Corneal examination Digital retinal photography Digital corneal photography Fundus fluorescein angiogram[a]

[a] Small number of subjects with possible retinal findings only.

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TABLE 3. Adverse events occurring in >5% of subjects on tafenoquine or mefloquine (prophylactic phase)[a]

Adverse event	No. (%) of subjects by AE severity and treatment group							
	Mild		Moderate		Severe		Total	
	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine
At least one AE	431 (88)	140 (86)	194 (39)	46 (28)	18 (4)	3 (2)	454 (92)	143 (88)
Gastrointestinal								
Gastroenteritis	109 (22)	36 (22)	80 (16)	17 (11)	6 (1)	0	182 (37)	51 (32)
Diarrhea	77 (16)	28 (17)	0	2 (1)	1 (<1)	0	77 (16)	30 (19)
Nausea	27 (6)	13 (8)	1 (<1)	0	0	0	28 (6)	13 (8)
Abdominal pain	19 (4)	11 (7)	5 (1)	3 (2)	1 (<1)	0	24 (5)	13 (8)
Vomiting	19 (4)	8 (5)	2 (<1)	1 (<1)	0	0	21 (4)	8 (5)
Musculoskeletal								
Injury	149 (30)	46 (28)	45 (9)	4 (3)	3 (<1)	2 (1)	178 (36)	49 (30)
Back pain	65 (13)	24 (15)	12 (2)	2 (1)	0	0	74 (15)	26 (16)
Arthralgia	52 (11)	17 (11)	9 (2)	1 (<1)	0	0	55 (11)	18 (11)
Respiratory								
URTI	97 (20)	30 (19)	6 (1)	2 (1)	0	0	101 (21)	32 (20)
Pharyngitis	24 (5)	2 (1)	2 (<1)	1 (<1)	0	0	25 (5)	3 (2)
Dermatological								
Rash	70 (14)	20 (12)	1 (<1)	1 (<1)	0	0	70 (14)	21 (13)
Fungal dermatitis	43 (9)	8 (5)	1 (<1)	0	0	0	44 (9)	8 (5)
Headache (constitutional AE)	59 (12)	18 (11)	2 (<1)	2 (1)	0	0	61 (12)	20 (12)
Viral infection	23 (5)	7 (4)	16 (3)	6 (4)	1 (<1)	0	39 (8)	13 (8)

[a] In total, there were 492 tafenoquine subjects and 162 mefloquine subjects. AE, adverse event; URTI, upper respiratory tract infection.

tafenoquine subjects but was absent in the 21 mefloquine subjects (Table 2). These changes were not associated with any visual disturbances and there were no differences between the groups in visual acuity, Amsler grid score, or Ishihara (color vision) score. All subjects with vortex keratopathy were followed up until resolution, with the incidence reducing to 39% at 3 months and 10% at 6 months; there was complete resolution by all subjects by 1 year. Based on the initial findings, fundoscopic examinations were carried out on 86 subjects at the 3-month postprophylaxis follow-up. Abnormalities (e.g., granularity/pigmentation of retinal pigment epithelium or hard drusen) were noted for 27 (39.1%) of 69 tafenoquine subjects and 4 (23.5%) of 17 mefloquine subjects. Retinal fluorescein angiograms were performed on 14 tafenoquine subjects and 1 mefloquine subject for whom possible retinal findings had been observed. Of these, 4 (28.6%) tafenoquine subjects and 1 (100%) mefloquine subject were considered possibly abnormal. However, review by an expert ophthalmology review board concluded that the retinal findings may well have been normal variations and that there was no evidence to support drug-related visual disturbances. It should be noted that fundoscopic examination of the retina at follow-up was not blinded, because the examination was carried out with the knowledge that corneal deposits were present and no baseline data were available for comparison.

In addition to undergoing phospholipidosis assessments, the safety subgroup also underwent methemoglobin assessment and electrocardiograms for assessment of QT interval. Mean methemoglobin levels increased by 1.8% in the tafenoquine group and by 0.1% in the mefloquine group at the end of prophylaxis, but by week 12 of follow-up, the increase in methemoglobin had resolved. In the tafenoquine group, there was a small reduction in the mean QT interval (difference of −4.5 ms; 95% CI, −9.7 to 0.7 ms), whereas a small increase in the interval was seen in the mefloquine group (difference of 1.6 ms; 95% CI, −12.1 to 15.4 ms) at the end of prophylaxis. There were no subjects for which there was a clinically dangerous prolongation of the QT interval. None of the safety findings impacted participants' well-being or was considered clinically significant.

Tolerability. During the prophylactic phase, 454 (91.9%) of 492 tafenoquine subjects and 143 (88.3%) of 162 mefloquine subjects reported at least one adverse event. The most common adverse events (occurring in >5% of subjects) are summarized in Table 3. There was no significant difference between the 2 treatment groups in the number or type of adverse events, with the most common events being gastroenteritis and injury, which occurred in >30% of subjects in both treatment groups. The majority of adverse events were mild or moderate in severity. In total, there were 21 severe adverse events (18 [4%] tafenoquine subjects and 3 [2%] mefloquine subjects). The most common severe events were gastroenteritis (6 [1.2%] tafenoquine subjects and 0 mefloquine subjects) and injury (3 [0.6%] tafenoquine subjects and 2 [1.2%] mefloquine subjects). During the relapse follow-up phase, 203 (41.3%) tafenoquine/placebo subjects and 53 (33.9%) mefloquine/primaquine subjects reported adverse events; however, there was no notable difference between the treatment groups in the incidence or nature of events.

In total, 64 (13.0%) tafenoquine subjects and 23 (14.2%)

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TABLE 4. Neuropsychiatric events in subjects on tafenoquine or mefloquine (prophylactic phase)[a]

Adverse event	No. (%) of subjects by AE severity and treatment group					
	Mild		Moderate		Total	
	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine
Vertigo	22 (5)	7 (4)	0	1 (<1)	22 (5)	8 (5)
Somnolence	12 (2)	6 (4)	0	0	12 (2)	6 (4)
Abnormal dreams	7 (1)	2 (1)	0	0	7 (1)	2 (1)
Dizziness	5 (1)	2 (1)	0	0	5 (1)	2 (1)
Insomnia	4 (<1)	3 (2)	1 (<1)	0	5 (1)	3 (2)
Abnormal coordination	2 (<1)	1 (<1)	0	0	2 (<1)	1 (<1)
Anxiety	2 (<1)	0	0	0	2 (<1)	0
Agitation	2 (<1)	0	0	0	2 (<1)	0
Euphoria	2 (<1)	0	0	0	2 (<1)	0
Tremor	2 (<1)	0	0	0	2 (<1)	0
Depression	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Paroniria	1 (<1)	0	0	0	1 (<1)	0
Amnesia	1 (<1)	0	0	0	1 (<1)	0

[a] In total, there were 492 tafenoquine subjects and 162 mefloquine subjects. There were no severe adverse events (AEs) of this type.

mefloquine subjects reported neuropsychiatric adverse events, the most common being vertigo, dizziness and various sleep disorders (Table 4). There was no significant difference between the treatment groups in the incidence and type of neuropsychiatric events, and all were reported as mild or moderate.

Fifteen subjects withdrew from the study as a result of adverse events (12 [2.4%] tafenoquine subjects and 3 [1.9%] mefloquine subjects). Four tafenoquine subjects sustained injuries requiring evacuation from the study area, while 2 experienced arthralgia (1 subject on each drug). Three tafenoquine subjects withdrew for possible treatment-related adverse events, namely, abdominal pain (severe), depression (moderate), and hyperesthesia (moderate). The incidences of severe adverse events in the 2 groups were comparable (18 [3.7%] tafenoquine subjects and 5 [3.1%] mefloquine subjects).

In total, during the prophylactic phase, 66 (13.4%) tafenoquine subjects and 19 (11.7%) mefloquine subjects had adverse events with a suspected/probable relationship to treatment (Table 5). There were no significant differences between the treatment groups in the incidence or nature of treatment-related adverse events during the prophylactic phase. Only 1 subject on tafenoquine reported a severe adverse event (diarrhea and abdominal pain) suspected to be related to treatment.

TABLE 5. Table of adverse events attributed as related to study drug during prophylactic phase in the safety population[a]

Adverse event	No. (%) of patients in treatment group	
	Tafenoquine (n = 492)	Mefloquine (n = 162)
At least one AE	66 (13.4)	19 (11.7)
Nausea	14 (2.8)	4 (2.5)
Vertigo	10 (2.0)	2 (1.2)
Diarrhea	9 (1.8)	3 (1.9)
Abdominal pain	7 (1.4)	2 (1.2)
Abnormal dreaming	6 (1.2)	1 (0.6)
Somnolence	6 (1.2)	1 (0.6)
Headache	3 (0.6)	2 (1.2)
Insomnia	3 (0.6)	2 (1.2)

[a] Events occurring in >1% of subjects are shown. AE, adverse event.

Efficacy. No symptomatic malarial infections occurred during the prophylactic phase in either treatment group. Smears collected from symptomatic subjects and during routine screening for malaria diagnosis were all negative. There were 4 cases (0.9%) of malarial infection in the tafenoquine group and a single case (0.7%) in the mefloquine group during the relapse follow-up phase (95% CI, −1.32 to 1.74; P = 1.0). All cases corresponded to *P. vivax* infection, which occurred between 16 and 20 weeks following the return from East Timor.

DISCUSSION

This phase III study describes the safety and tolerability of tafenoquine administered for malaria prevention in a nonimmune population of predominately young Caucasian males. Both tafenoquine and mefloquine were well tolerated. There were no clinically significant differences between hematological and blood chemistry results for the 2 treatment groups.

Assessment for phospholipidosis and its effects in a subgroup of 98 subjects showed at the end of the prophylactic phase a high incidence (93.2%) of mild vortex keratopathy (corneal deposits) in the tafenoquine group. Based on these findings, an independent expert ophthalmology board was asked to review the data. It concluded that the corneal changes were benign, fully reversible, and similar to those seen with several other drugs, including chloroquine, for which it is not considered to be a contraindication for continuous use (1). It also advised us that vision had not been impaired in any subject. A lack of baseline retinal photography data meant that the relevance of retinal findings could not be ascertained, but they reflected normal variability. Further assessment of the eye changes observed with tafenoquine will need to be undertaken to determine with certainty the overall significance of the observed changes and to clarify the retinal issues raised during the review.

As would be expected in a long-term study, the incidence of adverse events was high, with 92% of tafenoquine subjects and 88% of mefloquine subjects reporting one or more adverse events during the 6 months of prophylaxis. The majority of these events was mild or moderate in severity, and the events

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Use of the Quinoline anti-malarial drugs Mefloquine and Tafenoquine in the Australian Defence Force
Submission 1 - Supplementary Submission 1

were typical of the type of events expected in a population of soldiers on active duty (e.g., injury or gastroenteritis). The number of withdrawals from the study was low for a long-term study, also reflecting the nature of the study population. There were no significant differences in the occurrence of treatment-related adverse events, including gastrointestinal and neuropsychiatric disturbances between the 2 treatment groups.

Limited comparative data on the tolerability of tafenoquine used for prophylaxis are available. In adult black Kenyans, the incidences of adverse events for subjects on placebo and on weekly 200 mg tafenoquine for 13 weeks were similar (21). Relative to our findings, the study of the Kenyans reported a higher incidence of headache (24% versus 12.4%) but lower incidences of diarrhea (7% versus 15.7%) and rashes (4% versus 14.2%) with the same maintenance dose. However, such comparisons are difficult to make when the subject populations differ so markedly in ethnicity, nutritional status, culture, employment, and tolerance to medication.

Mefloquine was well tolerated by the Australian soldiers, which is in accordance with the results of other randomized, double-blind studies of military populations (2, 6, 17). No soldiers on mefloquine withdrew from the study due to treatment-related adverse events, and no more than 2% of the soldiers on either tafenoquine or mefloquine experienced drug-associated neuropsychiatric disturbances. Severe neuropsychiatric adverse events in European travelers on mefloquine have been reported (18, 20), but such events were not observed in the present study. Neuropsychiatric adverse events related to mefloquine use are reported to be more common in females (20), and the somewhat atypical distribution of participants in this study should be considered when generalizing these findings.

Without a placebo control, the exposure to malaria experienced by the Australian soldiers could not be directly estimated. As an indication of the malaria exposure that the soldiers probably encountered, 2 malaria prevalence surveys were conducted (January 2001 and April 2001) in 7 East Timorese villages (about 200 residents in each village), all within 1 km of where the soldiers were located (3). The surveys showed that malaria was present in 6 of the 7 locations, with point prevalence rates ranging from 0 to 35.3% (*P. falciparum*, 0 to 14.4%; *P. vivax*, 0 to 16%). In addition to this evidence, several studies have confirmed a high incidence of malaria in East Timor (8, 11–12, 14, 19). While these studies are not conclusive proof that subjects in the present study were exposed to malaria, it is highly likely that the soldiers were exposed to both *P. falciparum* and *P. vivax* malaria. Because no prophylactic failures occurred during the treatment phase in East Timor, both treatments appeared to be effective in suppressing malaria infections. During the 6-month relapse follow-up period, 4 (0.9%) subjects on tafenoquine/placebo and 1 (0.7%) subject on mefloquine/primaquine developed *P. vivax* infections. These findings indicate that tafenoquine and primaquine are equally effective in preventing *P. vivax* relapse when primaquine compliance is monitored and confirm the results of previous studies in Papua New Guinea (16) and East Timor (7). Although the relapse rates for primaquine and tafenoquine appear to be similar, tafenoquine offers a major advantage in that there is no need to take additional medication after leaving the endemic area if tafenoquine is used for prophylaxis.

In summary, tafenoquine at 200 mg weekly is safe and well tolerated in nonimmune Caucasian subjects following 6 months of prophylaxis. Although mild vortex keratopathy was seen in the subjects on tafenoquine, this was benign and fully reversible. The most frequently recorded treatment-related adverse events for both tafenoquine and mefloquine were gastrointestinal disturbances, and these tended to be mild or moderate. Both treatments fully suppressed malarial infections during prophylaxis, and less than 1% of subjects developed postexposure malaria after either completion of tafenoquine prophylaxis or primaquine treatment. Tafenoquine is an effective alternative weekly antimalarial that can be used without the need for further medication after leaving an endemic area.

ACKNOWLEDGMENTS

Tafenoquine Study Team members included Karl Rieckmann, Bob Cooper, Stephen Frances, Michael Reid, Alyson Auliff, Bruce Russell, Stephen McLeod-Robertson, John Staley, Kerryn Rowcliffe, John Ross, and Brian Putter from the Australian Army Malaria Institute, Keith Barker and Dominic Galvin from GlaxoSmithKline Research & Development Limited, and Ann Aultman from the U.S. Army Medical Materiel Development Activity.

We thank John Calagari, Stephen Ferndale, Damien Wood, and officers and soldiers of the 1st Battalion Group, Royal Australian Regiment, East Timor, who participated in the study for their support and cooperation. We are grateful to G. Dennis Shanks and Bob Cooper for commenting on the manuscript.

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P.P. and C.K. are employees of GlaxoSmithKline Research & Development Limited. For all other authors, there are no conflicts.

The opinions expressed are ours and do not necessarily reflect those of the Joint Health Command, Australian Defence Force, the U.S. Army, or any extant defense force policy.

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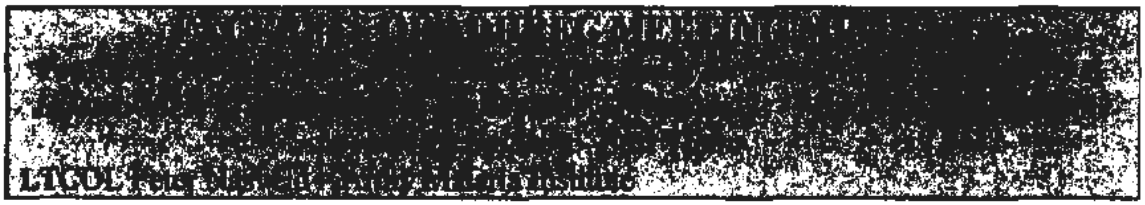

5 June 2000

4.h. Protocol 195/99 - Evaluation of Tafenaquine for the prophylaxis of malaria in non-immune Australian soldiers. This protocol has been resubmitted with the number 216/00. It will be used in the next wet season for a Battalion Group in a double blind controlled trial using a weekly capsule.

(5) PROTOCOL 216/00 – A RANDOMISED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR

Decision:
ADMEC decided that the consent form required to be reworded to include the usual provision that members can withdraw at any time "without detriment to my career or ongoing medical care." The correct contact details and address for ADMEC are to be used on the information sheet. Providing these requirements are met Committee agreed to approve the protocol.

For action:
Exec Sec

21 August 2000

(2) Protocol 216/00 – A Randomised, Double-Blind, Comparative Study To Evaluate The Safety, Tolerability And Effectiveness Of Tafenoquine And Mefloquine For The Prophylaxis Of Malaria In Non-Immune Australian Soldiers Deployed To East Timor.

22. The Committee requests that in future if amendments are extensive, changes be displayed using strikethrough, to clarify their context. Exec Sec is also to clarify with Major Kitchener that the nominal rolls of participants ADMEC requires for clinical trials is essentially the same as the American requirement, using the ADF service number as the identifier. Data is to be retained in accordance with privacy provisions for five years for non-intervention studies and fifteen years in the case of clinical studies.

Decision:
Committee agreed to approve the protocol providing the above requirements are met.

For action:
Exec Sec

27 November 2000

b. **Protocol 216/00 – A randomised, double-blind, comparative study to evaluate the safety, tolerability and effectiveness of Tafenoquine and Mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor**

(1) After inviting Major Kitchener to address the meeting again, Amendment 3 and Amendment 4 to the above protocol were discussed.

Decision
ADMEC agreed to accept the amendments.

For action:
Exec Sec

(2) Major Kitchener reported that of 13 serious adverse events reported from the study of 670 participants, only two gastro intestinal events could possibly relate to the administration of Tafenoquine.

Decision
ADMEC agreed to accept the report.

For action:
Exec Sec

26 February 2001

h. **Protocol 216/00 - A Randomised, Double-Blind, Comparative Study To Evaluate The Safety, Tolerability And Effectiveness Of Tafenoquine And Mefloquine For The Prophylaxis Of Malaria In Non-Immune Australian Soldiers Deployed To East Timor**

Decision
ADMEC agreed to accept the modification to the protocol. In addition, ADMEC decided to develop its own Serious Adverse Events form for use in the event that one was not otherwise provided by the researcher.

For action:
Exec Sec

13. ADMEC then considered and noted the following Progress reports:

f. **Protocol 216/00 - A Randomised, Double-Blind, Comparative Study To Evaluate The Safety, Tolerability And Effectiveness Of Tafenoquine And Mefloquine For The Propbylaxis Of Malaria In Non-Immune Australian Soldiers Deployed To East Timor;**

18 June 2001

d. Brief by Major Scott Kitchener, Officer in Charge: Clinical Trials AMI, and Lieutenant Commander Sonya Bennett, Research Officer AMI

5. The Chair then invited Major Kitchener and Lieutenant Commander Bennett to address ADHREC.

FOLIO 26

DEFENCE PERSONNEL EXECUTIVE

DEFENCE HEALTH SERVICE BRANCH

CP2-7-121, Department of Defence, CANBERRA ACT 2600

2000/7416/1
ADMEC 216/00
DHSB 690/2001

Lieutenant Colonel P.E. Nasveld
Senior Medical Officer 7th Brigade
c/- Australian Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

AUSTRALIAN DEFENCE MEDICAL ETHICS COMMITTEE (ADMEC) PROTOCOL 216/00: A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR

Dear Lieutenant Colonel Nasveld

1. Thankyou for submitting for protocol amendment number 6 dated 5th April 2001. The proposed amendments were considered by the Chairperson, Australian Defence Medical Ethics Committee on the 9th April 2001.

2. The ADMEC Executive has considered your protocol and has approved the amendment. As such the protocol is now cleared to proceed with these modifications in place.

6. If you have any queries regarding the decisions of ADMEC please call me on the number listed below.

Yours sincerely,

s22 [redacted]

Raphaela Jarvis
Assistant Executive Secretary
Australian Defence Medical Ethics Committee

12 April, 2001

CC: Ms. Kathie Mantine

Australian Defence Medical Ethics Committee

DEPARTMENT OF DEFENCE
CANBERRA ACT 2600

FACSIMILE TRANSMISSION / COVER

To:	From:
LTCOL P. Nasveld	Raphaela Jarvis Assistant Executive Secretary CP2-7-068
Fax:	**Fax:**
Phone:	**Phone:** [redacted]7
E-mail:	

Subject: ADEMC Approval of Amendments

Reference:	Date:	N° Pages (*Including cover*)
	12 Apr 01	2

MESSAGE:

LTCOL Nasveld,

Following is a copy of the letter indicating ADMEC's approval of Amendments No 6 to ADMEC Protocol 216/00. The original is in the post to Gallipoli Barracks.

Wishing you a very happy Easter,

s22 [redacted]

Raphaela

This facsimile remains the property of the Defence Organisation and is subject to the jurisdiction of Section 70 of the *Crimes Act 1914*. If you receive this facsimile in error, you are requested to immediately contact the sender by telephone so that arrangements can be made for the return of this document to the sender.

FOLIO 215

Jarvis, Raphaela

From:
Sent: Monday, 9 April 2001 16:27
To: Jarvis, Raphaela
Cc: Prescott, William R LTC USAMMDA
Subject: Sec: Unclassified 033 Amendement 6

Mac Word 3.0

Since see telecon AVM Bruce Short 1645 hrs 9 apr 01
SGADF happy with proposed amendment.

Raphaela,
Here albeit late is the amendment that concerns the final dose timings of the ADMEC 216/00 Protocol.
It has taken some time revisiting the modelling data to incorpoorate the levels currently being seen in our soldiers at 4, 8 and 16 weeks. We believe the model to be valid and as such there is an urgent requirement to have this change endorsed by the ADMEC Executive. The issue is one of safety therefore as the PI I can implement the change without formal approval under GCP guidelines - but feel we have endeavoured to maintain the highest research standards and so request that you acknowledge the receipt of this amendment and speak to the Surgeon General to obtain Executive Approval pending formal approval by the full committee on 23 April. Regretably that would be too late as the first troops leave Timor on 16 April 01 and I would like to have some formal acknowledgement before then. I would be happy to discuss this further with the SG or others if required but the attachment as provided by Protocol Development at SmithKline is self explanatory. My mobile number is 0419 478 370.
Thanks again and apologies for the lateness of this approach - but as you can see it only arrived over the weekend.
Pete

---------- Forwarded by AMI/Asnce-Em/au on 09/04/2001 14:07

[redacted] on 06/04/2001 16:33:32

To: s47F [redacted]
s47F [redacted]
cc:

Subject: 033 Amendement 6

Pete
Just got off the phone with s47F [redacted] and out of e-mail contact) and Ann and discussing the modelling data.
Attached is the Amendment of 6th April 2001 - which s47 is happy with.
Only change from the one you've seen of 5th April is on page 2 Rationale
For Change 1st paragraph: changed the protection from approximately 4 weeks to approximately 3 weeks to be consistent with following paragaph.

(See attached file: TQ 033 Amendment 6 FINAL.doc)
Hope you're OK with this.
All the best
Keith

24

A randomized, double-blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor

Protocol Number SB 252263/033
(ADMEC No. 216/00)

PROTOCOL AMENDMENT 6

Final Protocol Approval Date: 18th May 2000

Amendment 6: 5th April 2001

1. Rationale for change

Key features of tafenoquine are that it has significant liver stage activity on the *Plasmodium* parasite and a long plasma half life (around 2 to 3 weeks). This should allow dosing to be stopped at the time of leaving a malaria endemic area, unlike other currently available malaria prophylactics. Important in this is ensuring therapeutic plasma levels of tafenoquine are maintained to protect against any possible late blood stage parasites up to a period of approximately 3 weeks after leaving an endemic region. Previous work in a study with the Royal Thai Army, with PK analysis by the Australian Malaria Institute, suggest that the minimum therapeutic plasma level is around 50 ng/ml; allowing for a safety margin, 100 ng/ml is a reasonable minimum target tafenoquine plasma level to ensure protection.

In the current study, in order to build in the largest possible safety margin, taking a final dose of study medication within the 24 hours immediately prior to leaving the malarious area will ensure plasma levels are maintained for the longest possible period at or above 100 ng/ml. Modelling based on pharmacokinetic data suggests that *without* dosing on the day of leaving the endemic region up to 19% of subjects could have levels below 100 ng/ml at 3 weeks after leaving the endemic region, compared with up to 8% below 100 ng/ml at 3 weeks *with* the extra dose.

All subjects in study 033 have been receiving their regular weekly doses of study medication on a Sunday. Study subjects will, however, leave the malarious area on various days of the week. This amendment aims to ensure that if a subject is to be deployed out of the malarious area greater than 24 hours after their last regular scheduled dose, then they will receive an additional dose of study medication; this additional dose should be timed to be given in the 24 hours immediately prior to leaving the endemic region (ie. being deployed out of East Timor). Subjects who receive their last regular scheduled dose within the 24 hours immediately prior to leaving the endemic region will not need to receive an additional dose of study medication. The dates of the last dose of study medication and the date of leaving the endemic region will be recorded.

2. Section 1, Summary, page 8

Was:

.....The soldiers will be given (in a double-blind fashion) either a loading dose of daily 200mg tafenoquine over 3 days (total 600mg) followed by weekly 200mg tafenoquine for 6 months or a loading dose of 250mg mefloquine over 3 days (total 750mg) followed by weekly 250mg mefloquine for 6 months.

Is:

.....The soldiers will be given (in a double-blind fashion) either a loading dose of daily 200mg tafenoquine over 3 days (total 600mg) followed by weekly 200mg tafenoquine for 6 months or a loading dose of 250mg mefloquine over 3 days (total 750mg) followed by weekly 250mg mefloquine for 6 months; timing of the final dose of prophylaxis medication will be within the 24 hours immediately prior to leaving the endemic region.

3. Section 5a, Study Design, page 18

Was:

The study is a double-blind, randomized clinical trial comparing the effectiveness, safety and tolerability of tafenoquine and mefloquine for chemoprophylaxis of malaria infections in non-immune Australian Defence Force (ADF) personnel deployed to a malarious area. The prophylaxis regimens will include a loading dose during pre-deployment training in Australia of 600mg tafenoquine (200mg daily for three days) or 750mg mefloquine (250mg daily for three days). All volunteers will subsequently receive either 200mg tafenoquine or 250mg mefloquine weekly. The chemoprophylactic trial period ('prophylactic phase') is six months with a follow-up period of a further six months ('relapse follow-up phase').

is:

The study is a double-blind, randomized clinical trial comparing the effectiveness, safety and tolerability of tafenoquine and mefloquine for chemoprophylaxis of malaria infections in non-immune Australian Defence Force (ADF) personnel deployed to a malarious area. The prophylaxis regimens will include a loading dose during pre-deployment training in Australia of 600mg tafenoquine (200mg daily for three days) or 750mg mefloquine (250mg daily for three days). All volunteers will subsequently receive either 200mg tafenoquine or 250mg mefloquine weekly with a final dose of study medication to occur within the 24 hours immediately prior to leaving the endemic region. The chemoprophylactic trial period ('prophylactic phase') is six months with a follow-up period of a further six months ('relapse follow-up phase').

4. Section 7d v, Day 2, page 31

Final paragraph was:

After the final dose of the loading dose is taken, the next dose of study medication will be scheduled for day 7 after the first dose of the loading dose regimen. Thereafter, prophylactic medication will be dispensed to subjects on a weekly basis.

is:

After the final dose of the loading dose is taken, the next dose of study medication will be scheduled for day 7 after the first dose of the loading dose regimen. Thereafter, prophylactic medication will be dispensed to subjects on a weekly basis. Timing of the final dose of prophylactic medication will be such that it will occur within a 24 hour period immediately prior to leaving the endemic region; see Section 8b, Dosage and Administration for details.

5. Section 8b, Dosage and Administration, page 34

1st paragraph was:

On days 0 to 2 of the study, subjects will receive (with food) a loading dose of study medication (tafenoquine 200mg per day for 3 days or mefloquine 250mg per day for 3 days) followed by weekly doses (again with food) of 200mg tafenoquine or 250mg mefloquine for the duration of the prophylactic phase.

is:

On days 0 to 2 of the study, subjects will receive (with food) a loading dose of study medication (tafenoquine 200mg per day for 3 days or mefloquine 250mg per day for 3 days) followed by weekly doses (again with food) of 200mg tafenoquine or 250mg mefloquine for the duration of the prophylactic phase. Timing of the final dose of prophylactic medication will be such that it will occur within a 24 hour period immediately prior to leaving the endemic region.

Therefore, if a subject is due to be deployed out of the malarious area greater than 24 hours after their last regular scheduled dose, then they will receive an additional dose of study medication; this additional dose should be timed to be given in the 24 hours immediately prior to leaving the endemic region (ie. being deployed out of East Timor). Subjects who receive their last regular scheduled dose within the 24 hours immediately prior to leaving the endemic region will not need to receive an additional dose of study medication. The dates of the last dose of study medication and the date of leaving the endemic region will be recorded.

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FOLIO 20

2000/7416/1
ADMEC 216/00
DHSB 329/2001

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AUSTRALIAN DEFENCE MEDICAL ETHICS COMMITTEE (ADMEC) PROTOCOL 216/00: A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR

Dear Lieutenant Colonel Nasveld

1. Thankyou for submitting for protocol amendment number 5 dated 9th February 2001. The proposed amendments were considered by The Australian Defence Medical Ethics Committee on 26th February 2001. The members of the Committee are listed in Annex A.

2. One Committee member s47F was absent from the meeting. The Australian Defence Medical Ethics Committee complies with the National Statement on Ethical Conduct in Research Involving Humans, 1999 and as such, in accordance with paragraph 2.16, the Chairman was satisfied that the absent member had received all papers and had had an opportunity to have his views recorded and considered.

5. ADMEC has considered your protocol and has approved the amendment. As such the protocol is now cleared to proceed with these modifications in place.

6. If you have any queries regarding the decisions of ADMEC please call me on the number listed below.

Yours sincerely,

s22

M. Blenkin
Lieutenant Commander
Executive Secretary
Australian Defence Medical Ethics Committee

1 March, 2001

Annex:
A. Australian Defence Medical Ethics Committee: Qualifications of Members

Australian Defence Medical Ethics Committee: Qualifications of Members

s47F

FOLIO 17

A randomized, double-blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor

Protocol Number SB 252263/033
(ADMEC No. 216/00)

PROTOCOL AMENDMENT 5

Final Protocol Approval Date: 18th May 2000

Amendment 5: 9th February 2001

1. Rationale for change

This amendment deals with two changes to the protocol.

The first change was considered necessary due to the highly unusual nature of the study setting, namely a militarised zone far removed from the infrastructure and support of a normal civilian setting. It has become apparent that soldiers are hospitalised for conditions that would not, under normal circumstances in a civilian setting, lead to hospitalisation; isolation from alternative facilities and a need to ensure troops are rapidly returned to optimal fitness means that interventions can occur that otherwise would not. This has, effectively, lead to the over-reporting of adverse events as Serious Adverse Events, and this amendment is designed to minimise this over-reporting.

The second change deals with the re-scheduling of the first visit of the Relapse Follow-up Phase from Week 6 to Week 2. It was considered more appropriate, and less of a burden to study subjects, to conduct this visit immediately after the completion of eradication medication and before subjects go away on leave. In addition, it is likely that many subjects would not have returned from leave by week 6 of the Relapse Follow-up Phase, and thus would have violated the protocol by attending this visit late, or not attending at all. Therefore, throughout the protocol, wherever the Week 6 Relapse Follow-up visit is referred to, this should now be considered to mean the Week 2 Relapse Follow-up visit. The major change to the protocol regarding this part of the amendment is detailed below.

2. Section 11 e, Serious Adverse Experiences, page 39

Was:

** Hospitalisation

AEs requiring hospitalisation should be considered serious. Hospitalisation for, e.g, elective surgery which is not the result of an AE (eg elective surgery for a pre-existing condition) need not be considered an AE and should be recorded on the medical/surgical procedures form. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria. In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

Is:

Hospitalisation:

Hospitalisation signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or received treatment that would not have been appropriate in the physician's office or in an out-patient setting.

A serious AE does **not** include hospitalisation for:

- Elective surgery or routine treatment/procedures related to a pre-existing condition that did not worsen.
- Non-medical reasons (i.e. social admissions, hospitalisations for social, convenience or respite care). This includes admissions to hospital for individuals who are considered unfit for military duty due to events, the medical nature and/or severity of which, in a civilian setting, would NOT routinely lead to hospitalisation.

NOTE: If anything untoward (i.e. complications) occurs during a hospitalisation as described above, this must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

3. Section 7 d viii, Week 6 of relapse follow-up phase, page 32

Was:

viii Week 6 of relapse follow-up phase

This visit will be performed in barracks in Australia, after subjects return from leave. At this visit, the following assessments will be performed and details recorded in the CRF.

- adverse events
- concomitant medication
- malaria status

NOTE: In the period leading up to this visit, additional blood samples may be collected for safety purposes if considered necessary by an investigator or co-investigator. All results will be recorded in the CRF.
Any subjects who have symptoms of malaria or who have been diagnosed with malaria will have blood smears taken (see section 7 c ii,Measurement of Parasitaemia and Diagnosis of Malaria). Full details will be recorded in the CRF.

For this visit, a 'window' of ± 2 weeks is allowable.

Is:

viii Week 2 of relapse follow-up phase

This visit will be performed in barracks in Australia, after subjects have completed their course of eradication medication, and before going on leave. At this visit, the following assessments will be performed and details recorded in the CRF.

- adverse events
- concomitant medication
- malaria status

NOTE: In the period leading up to this visit, additional blood samples may be collected for safety purposes if considered necessary by an investigator or co-investigator. All results will be recorded in the CRF.
Any subjects who have symptoms of malaria or who have been diagnosed with malaria will have blood smears taken (see section 7 c ii,Measurement of Parasitaemia and Diagnosis of Malaria). Full details will be recorded in the CRF.

For this visit, a 'window' of an additional 14 days after week 2 is allowable.

FOLIO 16

DEFENCE PERSONNEL EXECUTIVE
DEFENCE HEALTH SERVICE BRANCH
CP2-7-121, Department of Defence, CANBERRA ACT 2600

2000/7416/1
ADMEC 216/00
DHSB 2649/2000

227772
Lieutenant Colonel P.E. Nasveld
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Sydney NSW 2890

AUSTRALIAN DEFENCE MEDICAL ETHICS COMMITTEE (ADMEC) PROTOCOL 216/00: A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR

Dear Lieutenant Colonel Nasveld

1. Thankyou for submitting for protocol amendments 3 and 4 dated 28 September 2000 and 23 November 2000 respectively.

2. The proposed amendments were both considered by The Australian Defence Medical Ethics Committee on 27 November 2000. Committee members present were:

s47F

3. The qualifications of the Committee members and the positions held within the Committee are in Annex A.

4. Two Committee members s47F and s47F left the meeting prior to its official closure. They were, however, present for the deliberations on the proposed amendments to this protocol. .

5. Amendment 3 dated 28 September 2000 and amendment 4 dated 23 November 2000 were both approved at the above meeting. As such the protocol is now cleared to proceed with these modifications in place.

6. If you have any queries regarding the decisions of ADMEC please call me on the number listed below.

Yours sincerely,

s22 [redacted]

M. Blenkin
Lieutenant Commander
Executive Secretary
Australian Defence Medical Ethics Committee

30 November, 2000

Annex:
A. Australian Defence Medical Ethics Committee: Qualifications of Members

AN A
DCP 2849/2000

Australian Defence Medical Ethics Committee:

Members Present at Meeting 27 NOV 00

[redacted]

s22 [redacted]

A randomized, double-blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor

Protocol Number SB 252263/033
(ADMEC No. 216/00)

PROTOCOL AMENDMENT 3 ✓

Final Protocol Approval Date: 18th May 2000

Amendment 3: 28th September 2000

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9. SECTION 14 E III, SECONDARY EFFICACY ANALYSIS, PAGE 46 11

1. Overall Rationale

This amendment was produced as a result of the unexpected results seen in the phase III Kenya study, 252263/030 (for full details please refer to document sent to relevant Ethics Committees and Regulatory bodies, 'Tafenoquine Study 030 Update: Regulatory and IRB Summary Report').

It was considered necessary to change the primary efficacy end-point of this study from a single positive smear (either with or without symptoms of malaria) to a single positive smear with signs and symptoms consistent with malaria. This was done to ensure that no subject would be withdrawn from the study as a result of parasitaemia that did not lead to clinical signs and symptoms of the disease, which would not otherwise be considered clinically relevant. This is consistent with the normal clinical care of Australian Defence Force personnel when deployed to malarious regions, so does not include any increased risk to subjects involved in this study. Only slides from subjects experiencing symptoms consistent with malaria will be read immediately on site, in order to confirm a clinical diagnosis and so that appropriate therapeutic intervention can take place.

A single positive smear with or without signs and symptoms consistent with malaria will now become a secondary end-point in the study. Asymptomatic parasitaemia is expected to be a rare phenomenon since, in the malaria-naïve subjects included in this study, parasitaemia is normally associated with symptoms of disease. This change is therefore not expected to effect the power of the study with respect to the primary efficacy end-point. The secondary end-point is being included in order to be consistent with the remainder of the Phase III clinical development program where other populations with immunity to malaria will be included and where asymptomatic *Plasmodial* infections are possible. Scheduled slides associated with monitoring for any asymptomatic parasitaemia will be read on completion of the prophylactic phase.

The time period for the primary efficacy end-point has been changed from 'during prophylactic study drug administration up to and including the day of the last dose of eradication medication' to 'during prophylactic study drug administration up to and including the day of the first dose of eradication medication'. This is in order to exclude the period of primaquine administration in the mefloquine treatment group, given for vivax eradication, which would otherwise confound the assessment of the effectiveness of tafenoquine and mefloquine as prophylactic agents.

As the rationale for the changes in this amendment has been described above, changes to the text of the protocol will only be listed below.

2. Summary of protocol, page 3

Was:

PROCEDURES: **OUTCOME**	*Outcome measures* – positive malaria slide during the chemoprophylaxis phase and the 6 months following departure from East Timor
LABORATORY	Assessment of Parasitaemia Plasma Drug Levels Haematology Biochemistry G6PD Deficiency Screening Pregnancy testing Assessment of methaemoglobinaemia and phospholipidosis

is:

PROCEDURES: **OUTCOME**	*Outcome measures* – positive malaria slide (with clinical signs and symptoms consistent with malaria infection) during the chemoprophylaxis phase and the 6 months following departure from East Timor
LABORATORY	Assessment of Parasitaemia Plasma Drug Levels Haematology Biochemistry G6PD Deficiency Screening Pregnancy testing Assessment of methaemoglobinaemia and phospholipidosis

3. Study Flow Chart, page 4

Amendment to footnote.

Was:

Samples for plasma drug concentration will be taken at varying times relative to dosing (day 1, 3, 5 and 7 after weekly dose of study medication). If a subject develops parasitaemia during the prophylactic phase, one additional sample will be collected at the time of developing parasitaemia and a second 12 weeks later. For any subject who develops parasitaemia during the relapse follow-up phase (up to week 12 only) a single sample will be collected at the time of diagnosis.

Is:

Samples for plasma drug concentration will be taken at varying times relative to dosing (day 1, 3, 5 and 7 after weekly dose of study medication). If a subject develops clinical malaria during the prophylactic phase, one additional sample will be collected at the time of diagnosis and a second 12 weeks later. For any subject who develops clinical malaria during the relapse follow-up phase (up to week 12 only) a single sample will be collected at the time of diagnosis.

4. Section 1, Summary, page 8

First part of third paragraph was:

The study population will be an Australian Defence Force (ADF) infantry battalion on peace-monitoring duties in East Timor. The soldiers will be given (in a double-blind fashion) either a loading dose of daily 200mg tafenoquine over 3 days (total 600mg) followed by weekly 200mg tafenoquine for 6 months or a loading dose of 250mg mefloquine over 3 days (total 750mg) followed by weekly 250mg mefloquine for 6 months. Drug administration will be observed and subjects will be monitored for malaria parasitaemia by regular blood smears or immediately when malaria symptoms are suspected. Haematology.....

Is:

The study population will be an Australian Defence Force (ADF) infantry battalion on peace-monitoring duties in East Timor. The soldiers will be given (in a double-blind fashion) either a loading dose of daily 200mg tafenoquine over 3 days (total 600mg) followed by weekly 200mg tafenoquine for 6 months or a loading dose of 250mg mefloquine over 3 days (total 750mg) followed by weekly 250mg mefloquine for 6 months. Drug administration will be observed. Subjects developing clinical signs and symptoms consistent with malaria infection at <u>any</u>

time during this phase will have blood smears performed for confirmation of the diagnosis. Haematology.....

5. Section 7 b, General Instructions, page 22

Third paragraph was:

Blood smears will be identified by their unique subject number for screening by a blinded microscopist, recording the number of parasites per 500 white cells counted. Prophylaxis failure will be defined by the development of a single positive blood smear for malaria parasites (either with or without symptoms). Any volunteer who does develop malaria during the study will be treated according to current clinical practice (e.g quinine plus doxycycline for *P.falciparum* infections or chloroquine for *P.vivax* infections) but withdrawn from the study.

Volunteers will be issued with an identification card indicating their involvement in the study. The card will contain guidelines to treating Medical Officers on the commencement of treatment, and will contain a pager number for contacting the duty Clinician of AMI.

The study ID card will also advise the treating Medical Officer of the requirements to provide AMI with confirmatory blood slides taken when a volunteer presents with fever.....

Is:

Subjects developing clinical signs and symptoms consistent with malaria at any time during the prophylaxis phase will have blood smears taken for confirmation of the diagnosis. Prophylaxis failure will be defined by the development of a single positive blood smear for *Plasmodia spp.* associated with clinical signs and symptoms consistent with a malaria infection, otherwise termed 'clinical malaria' for the purposes of this protocol. Any volunteer who does develop 'clinical malaria' during the study will be treated according to current clinical practice (e.g quinine plus doxycycline for *P.falciparum* infections or chloroquine for *P.vivax* infections) and withdrawn from the study. See section 7.c.ii for details of the assessment of parasitaemia and the diagnosis of malaria.

Volunteers will be issued with an identification card indicating their involvement in the study. The card will contain guidelines to treating Medical Officers on the commencement of treatment, and will contain a pager number for contacting the duty Clinician of AMI.

During the Relapse Follow-up, the subject's ID card will advise any treating Medical Officer of the requirements to provide AMI with confirmatory blood slides taken when a volunteer presents with fever.....

6. Section 7 c ii, Measurement of Parasitaemia, page 24

Title changed to "Measurement of Parasitaemia and Diagnosis of Malaria"

Was:

Thick and thin blood films for malaria diagnosis will be obtained from the venous sample (see (i) above) at screening to exclude malaria at the point of entry. Additional smears* will he performed at scheduled visits and on any day a volunteer presents to a medical facility complaining of fever or experiencing any other clinical signs consistent with malaria. All smears will be read initially by the treating facility and then forwarded to AMI for confirmation by a microscopist "blinded" to both study treatment and the previous reader's result. Thick and thin blood films will be stained with Giemsa and evaluated by standard techniques. A total of 200 high-power fields will be viewed before a sample is declared negative. Parasite counts will be expressed per 500 white cell count.

Disagreements between the treating facility reading of the slide and AMI will be adjudicated by a third microscopist. If two microscopists agree that the blood smear is positive, then that volunteer will be classified as a failure of prophylaxis.

If symptoms of malaria are present at the time of diagnosis of malaria, this will be recorded in the CRF.

* Smears will also be performed on any subject who contracts Rickettsia, prior to commencing treatment with doxycycline.

Is:

Thick and thin blood films for malaria diagnosis will be obtained from the venous sample (see (i) above) or by finger prick and will be stained with Giemsa and evaluated by standard techniques. Smears will be taken at screening to exclude malaria at the point of entry. Additional smears* will be performed at scheduled visits and on any day a volunteer presents to a medical facility complaining of fever and/or experiencing any other clinical signs and symptoms consistent with malaria.

For subjects presenting at any time during the prophylaxis phase with signs and symptoms suggestive of malaria, blood smears will be read immediately by

microscopists at the study site. Such cases will have serial confirmatory slides taken and read over at least 3 consecutive days following the onset of signs and symptoms until *Plasmodium spp.* are identified or an alternative diagnosis is made

All other blood smears collected at scheduled visits will not be read at the study site, but will be forwarded to AMI where they will be stored until they are microscopically evaluated for the presence of *Plasmodium spp.* These slides will be assessed after all subjects have completed the prophylactic phase.

All slides from cases of suspected malaria presenting in the field will be read separately by two microscopists ('Reader 1' and 'Reader 2'), each of whom will be 'blinded' to both study treatment and the other reader's result. A total of 200 high-power fields will be viewed before a sample is declared negative. However, where symptoms are present, more than 200 fields may be read in order to confirm the diagnosis. Parasite counts will be expressed per 500 white cell count. In the case of a disagreement between Reader 1 and Reader 2 on the reading of a slide, the slide will be read by a third microscopist (the 'Arbitrator'). The arbitrator reading will be taken as final.

Presence of clinical signs and symptoms of malaria along with a blood smear declared positive for *Plasmodia spp.*, using the procedure outlined above, will be classified as a case of 'clinical malaria' for the purposes of this study.

If, during the prophylaxis phase of the study, a subject has clinical malaria (as defined in the paragraph above) then they will be classified as having met the primary efficacy end-point for the study (see section 14 d i). Details of the smear results and the presence of symptoms should be recorded in the CRF. These cases of clinical malaria will be withdarwn from the prophylaxis phase of the study treated with appropriate therapy (see section 7b for details).

During the Relapse Follow-up, the subjects' study ID cards will advise any treating Medical Officer of the requirements to provide AMI with confirmatory blood slides taken when a volunteer presents with fever, and for three consecutive days following onset of fever. Should treatment be initiated following confirmation of malaria by a regional laboratory, instructions for the collection of a plain and an EDTA sample of venous blood for forwarding to AMI (and thence to SB where necessary) for *Plasmodium* speciation (via Polymerase Chain Reaction techniques) and drug level analysis will also be included. Additionally, serial blood slides to determine clearing of parasitaemia will be detailed. The duty clinician at AMI will arrange transport of all samples to AMI by courier. Clinical malaria (as defined above) will also be the efficacy end-point for the relapse follow-up phase. This diagnosis will be obtained either through direct review of slides or an appropriate microscopic diagnostic report from the reporting

laboratory, along with review of clinical notes for confirmation of concurrent signs and symptoms consistent with a malaria infection.

* Smears will also be performed on any subject who contracts Rickettsia, prior to commencing treatment with doxycycline.

7. Section 7 c iv, Plasma drug concentration, page 25

Was:

Note: Two additional blood samples will be taken for measurement of plasma drug concentration from any subject diagnosed with malaria during the prophylaxis phase of the study. The first will be at the time of developing parasitaemia and the second 12 weeks later at the subject's final safety follow-up visit. For any subject who develops parasitaemia during the relapse follow-up phase (up to week 12 only) a single sample will be collected at the time of diagnosis.

Is:

Note: Two additional blood samples will be taken for measurement of plasma drug concentration from any subject diagnosed with clinical malaria during the prophylaxis phase of the study. The first will be at the time of diagnosis of clinical malaria and the second 12 weeks later at the subject's final safety follow-up visit. For any subject who develops clinical malaria during the relapse follow-up phase (up to week 12 only), a single sample will be collected at the time of diagnosis.

8. Section 14 d i, Endpoints (primary and secondary efficacy variables), page 43

Was:

Primary Efficacy Variable:

At the end of the prophylaxis treatment period, the prophylactic outcome for each subject will be derived as follows:

Prophylactic Success: No single positive smear during prophylactic study drug administration (tafenoquine/ mefloquine) up to and including the day of the last dose of eradication medication (placebo/ primaquine).

Prophylactic Failure: Single positive smear during prophylactic study drug administration (tafenoquine/ mefloquine) up to and including the day of the last dose of eradication medication (placebo/ primaquine).

Secondary Efficacy Variables:

The secondary variables are

- number of subjects experiencing malaria at any time during the study
- number of subjects with single positive smear (*P. falciparum* only) during prophylactic study drug administration up to and including the day of the last dose of eradication medication
- number of subjects with single positive smear (*P. vivax* only) during prophylactic study drug administration up to and including the day of the last dose of eradication medication
- time to single positive smear (all species) at any time during the study (prophylactic phase plus 6 months relapse follow- up phase).

Additionally the number of subjects with parasites of species other than *P. falciparum* and *P.vivax*, the number of subjects who test positive at different time points and the number of subjects with symptomatic vs. asymptomatic parasitemia will be summarised.

Is:

Primary Efficacy Variable

At the end of the prophylaxis treatment period, the prophylactic outcome for each subject will be derived as follows:

Prophylactic Success: No clinical malaria (single positive smear with concurrent clinical signs and symptoms consistent with malaria infection) during prophylactic study drug administration (tafenoquine/ mefloquine) up to and including the day of the first dose of eradication medication (placebo/ primaquine).

Prophylactic Failure: Clinical malaria (single positive smear with concurrent clinical signs and symptoms consistent with malaria infection) during prophylactic study drug administration (tafenoquine/ mefloquine) up to and including the day of the first dose of eradication medication (placebo/ primaquine).

Secondary Efficacy Variables

The secondary variables are

- number of subjects experiencing clinical malaria at any time during the study (prophylactic phase plus 6 months relapse follow- up phase).
- number of subjects with a single positive smear (with or without clinical signs/symptoms) during prophylactic study drug administration up to and including the day of the last dose of eradication medication.
- number of subjects with clinical malaria (*P. falciparum* only) during prophylactic study drug administration up to and including the day of the last dose of eradication medication
- number of subjects with single positive smear (*P. falciparum* only) with or without clinical signs/symptoms during prophylactic study drug administration up to and including the day of the last dose of eradication medication
- number of subjects with clinical malaria (*P. vivax* only) during prophylactic study drug administration up to and including the day of the last dose of eradication medication
- number of subjects with single positive smear (*P. vivax* only) with or without clinical signs/symptoms during prophylactic study drug administration up to and including the day of the last dose of eradication medication
- time to clinical malaria (all species) at any time during the study (prophylactic phase plus 6 months relapse follow- up phase).
- time to single positive smear (all species) with or without clinical signs/symptoms during prophylactic study drug administration up to and including the day of the last dose of eradication medication

Additionally the number of subjects with clinical malaria of species other than *P. falciparum* and *P.vivax*, the number of subjects with single positive smear (with or without clinical signs/symptoms) of species other than *P. falciparum* and *P. vivax*, the number of subjects who have clinical malaria at different time points (total and by species), and the the number of subjects who have single positive smear with or without clinical signs/symptoms (total and by species) at different time points will be summarised.

9. Section 14 e iii, Secondary efficacy analysis, page 46

Was:

For the secondary efficacy variables number of subjects with malaria at any time in the study, number of subjects with a single positive smear (P. *falciparum* only) during the prophylactic phase and number of subjects with a single positive smear (*P. vivax* only) during the prophylactic phase, the 95% stratified confidence interval for treatment difference in proportions as described above will be presented. Again, in each case to confirm the appropriateness of using a stratified

confidence interval approach an analysis testing for a treatment by company interaction will be performed.

For time to malaria, a Kaplan- Meier curve will be produced showing the cumulative survival rates for each treatment group.

Is:

For each of the secondary efficacy variables

- number of subjects with a single positive smear (with or without clinical signs/symptoms) during prophylactic study drug administration
- number of subjects with clinical malaria at any time in the study
- number of subjects with clinical malaria (*P. falciparum* only) during prophylactic study drug administration
- number of subjects with a single positive smear with or without clinical signs/symptoms (*P. falciparum* only) during prophylactic study drug administration
- number of subjects with clinical malaria (*P. vivax* only) during prophylactic study drug administration and
- number of subjects with a single positive smear with or without clinical signs/symptoms (*P. vivax* only) during prophylactic study drug administration,

the 95% stratified confidence interval for treatment difference in proportions as described above will be presented. Again, in each case to confirm the appropriateness of using a stratified confidence interval approach an analysis testing for a treatment by company interaction will be performed.

For time to clinical malaria at any time during the study, and time to single positive smear with or without clinical signs/symptoms during the prophylactic phase, a Kaplan-Meier curve will be produced showing the cumulative survival rates for each treatment group (total and by species).

A randomised, double blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor.

Protocol Number SB 252263/033
(ADMEC No. 216/00)

PROTOCOL AMENDMENT 4

Final Protocol Approval Date: 18th May 2000-11-23

Amendment 4: 23rd November 2000

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Overall Rationale

This amendment was produced as a result of matching the practical aspects of implementing the study against the final protocol. It is intended to reduce the number of protocol violations which would otherwise need to be documented, without impacting on the intent or quality of the study.

The study is being conducted in an operational setting in East Timor. Difficulties include the provision of reliable power, communication, and access to volunteers scattered throughout the Australian Battallion (AUSATT) Area of Operations (AO). The proposed amendments deal with these limitations with the intent of reducing administrative load.

1. Section 7 b – General Instructions, page 23

First part of paragraph 4 was:

Volunteers will be issued with an identification card indicating their involvement in the study. The card.....

Is:

Volunteers will be issued with a stamped "dogtag" indicating their subject number in the trial. Additionally, they will be issued with an identification card prior to the commencement of the relapse follow up phase, indicating their involvement in the trial.

2. Section 7 c. i. – Collection and preparation of blood samples

Paragraph 4 was:

All blood samples will be refrigerated in a portable fridge at 4°C. From the 4ml EDTA tube, two blood smears will be prepared followed by haematological analysis. The remaining.....serum. Remaining plasma and serum will be stored (at -20°C whilst in East Timor and at -70°C n Australia) until analysed. Drug concentration analysis will be performed on the remaining plasma.

Is:

All blood samples will be refrigerated in a portable fridge (2-8°C) or on wet ice. From the 4ml EDTA tube haematological analysis will be performed as well as two blood smears being prepared. The remaining.....serum. Remaining plasma and serum will be stored (at -20°C to -35°C in East Timor and at -60°C to -80°C in Australia) until analysed. Drug concentration analysis will be performed on the remaining plasma.

Paragraph 5 was:

To allow for the analysis of population pharmacokinetics (PK), blood samples will be collected from all study subjects on pre-determined days on each of the assessment weeks. The .....

Is:

To allow for the analysis of population pharmacokinetics (PK), whenever possible blood samples will be collected from study subjects on predetermined days after dosing on each of the assessment weeks. The .....

Section 7 c. vii. Haematology – page 28

Paragraph 1 was:

Samples for haematology assessment will be taken at screening, day 2 and weeks 4,8,16 and 26 of the prophylaxic phase. The following haematology tests will be performed using an auto-analyser, with manual differentiation performed on any abnormal findings:

Is:

Samples for haematology assessment will be taken at screening, day 2 and weeks 4,8,16 and 26 of the prophylaxic phase. The following haematology tests will be performed using an auto-analyser, with manual differentiation performed on any clinically significant abnormal findings:

Section 7 c. xii. Physical Examination – page 30

Paragraph 1 was:

A full physical examination will be performed on study entry, at the end of the prophylactic phase (or premature withdrawal) and after 12 weeks of the relapse follow-up phase.

Is:

A pre-deployment check including review of Unit Medical Records (UMR) will be performed on study entry. When clinically indicated a physical examination will be conducted. Similar reviews will be conducted at either the premature withdrawal of a subject from the study or the termination of the prophylactic phase. A final review will be conducted after 12 weeks of the relapse follow-up phase.

Section 7 d. vi. Weeks 4,8 and 16 of prophylactic phase – page 32

Last paragraph was:

For each of these visits, a 'window' of ± 10 days is allowable.

Is:

For each of these visits, a 'window' of ± 14 days is allowable.

Section 7 d. viii. Week 6 of relapse follow-up phase – page 33.

Last paragraph was:

For this visit, a 'window' of ± 2 weeks is allowable.

Is:

For this visit, a 'window' of ± 3 weeks is allowable.

Section 7 d. ix. Week 12 of relapse follow-up phase – page 33.

Last paragraph was:

For this visit, a 'window' of ± 2 weeks is allowable.

Is:

For this visit, a 'window' of ± 3 weeks is allowable.

Section 8 f. Storage – page 35

Paragraph 2 was:

All drug supplies will be kept by the Platoon Sergeant in a locked container at the study site. The Platoon Sgt has no medical qualifications above first aid training.

Medication will be stored by AMI with only 4 weeks supply at a time being released forward for each volunteer, under the control of the Platoon Sergeant. In Company base areas and Headquarters rear areas this function will be performed by Medics and Regimental Aid Post staff. AMI staff will undertake roving monitoring each week and weekly checks will be conducted for all volunteers by AMI staff.

Is:

Individual volunteers will be responsible for security of their issued medication blister pack. When individuals are on active patrol duties, they may dispense sufficient medication to cover the duration of the patrol into labelled medication vials provided by AMI.

Remaining medications will he stored by AMI, with only individual blister packs of 4 weeks being released forward to each volunteer. Spare blister packs will be held by AMI in the event of loss. AMI staff will undertake opportunity roving monitoring of the condition of the blister packs weekly.

Section 8 g. Drug Accountability – page 36

Paragraph 1 was:

On delivery.....confirm receipt. Al study medication must only be dispensed to study subjects in accordance with the protocol and any unused medication must be returned to SB at thc end of the study.

Is:

On delivery.....confirm receipt. Al study medication must only be dispensed to study subjects in accordance with the protocol and any unused medication must be returned to SB, or disposed of in accordance with their written direction, at the end of the study.

Paragraph 2 was:

Drug accountability records must be maintained.....closing of the study. Weekly checking fulfils the requirement for drug accountability records to be maintained throughout the study so there is a perpetual reconciliation of study supplies.

Is:

Drug accountability records must be maintained.....closing of the study. Blister packs will be retrieved when the 4 weeks of medication is completed and a new 4 week pack dispensed. Reconciliation between unused trial medication returned and the Study Medication Antimalarial Roll Book will be conducted and recorded on the Drug Audit Log.

Section 11 e. Serious Adverse Events – Reporting Serious Adverse Experiences – page 40.

Paragraph 2 was:

In addition, serious and unexpected adverse experiences must be immediately reported by telephone (and followed up by fax) to:

Is:

In addition, serious and unexpected adverse experiences which are drug related must be immediately reported by telephone (and followed up by fax) to:

Paragraph 4 was:

The Executive Secretary of the Australian Defence Medical Ethics Committee (ADMEC) must be kept informed of all SAEs which occur during the study. Contact details are as follows:

Is:

The Executive Secretary of the Australian Defence Medical Ethics Committee (ADMEC) must be kept informed of all SAEs which occur during the study. Serious adverse experiences, which are unexpected and drug related are to be reported by

telephone or facsimile within 3 days. All other SAE are to be reported in the required 6 monthly reports. Contact details are as follows:

Section 12 a. Subject Completion and Withdrawal – page 41.

Paragraph 2 was:

For the prophylactic phase, ...at week the 24 visit of the relapse follow-up phase.

Is:

For the prophylactic phase, ...at the 26 week visit of the relapse follow-up phase.

Section 15 d. Case Report Form Instructions – page 49.

Paragraph 2 was:

CRFs will be .....to ensure that CRFs (and subject diary cards) are .....

Is:

CRFs will be .....to ensure that CRFs are .....

Section 15 h. Confidentiality and Publication – page 52.

Paragraph 2 was:

The sponsor .....has seen and agreed the proposed publication/presentation.

Is:

The sponsor .....has seen and agreed to the proposed publication/presentation.

FOI 20

DEFENCE PERSONNEL EXECUTIVE

DEFENCE HEALTH SERVICE BRANCH

CP2-7-121, Department of Defence, CANBERRA ACT 2600

2000/7416/1
ADMEC 216/00
DHSB 2230/2000

Lieutenant Colonel P.E. Nasveld
Senior Medical Officer 7th Brigade
c/- Australian Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

AUSTRALIAN DEFENCE MEDICAL ETHICS COMMITTEE (ADMEC) PROTOCOL 216/00: A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR

Dear Lieutenant Colonel Nasveld

1. Thankyou for your request for an approval summary for this protocol.

2. The original submission marked "Final Protocol" and dated 18 May 2000 was first considered on the 5th June 2000 by The Australian Defence Medical Ethics Committee. Committee members present were:

s47F [redacted]

3. One Committee member, Colonel Peter Warfe, CSC was absent from the 5th June 2000 meeting. The Australian Defence Medical Ethics Committee complies with the National Statement on Ethical Conduct in Research Involving Humans, 1999 and as such in accordance with paragraph 2.16, the Chairman was satisfied that the absent member had received all papers and had had an opportunity to have his views recorded and considered.

4. Approval of the protocol was considered pending until some minor amendments detailed in ADMEC Letter 1302/2000 dated 9 Jun 2000 were made. The Secretariat received the amendments by email from dated 13 Jun 2000. The amended Information/Consent Form had not been designated a version number or date. The Protocol was approved to proceed in ADMEC letter 1326/2000 dated 14 Jun 2000.

5. Amendments 1 and 2 dated 2 Aug 2000, as required by the HSRRB, were considered by the Australian Defence Medical Ethics Committee on the 21st August 2000. Committee members present were:

s47F [redacted]

6. One Committee member s47F [redacted] was absent from the discussion of the Amendments 1 and 2 at the 21st August 2000 meeting. The Australian Defence Medical Ethics Committee complies with the National Statement on Ethical Conduct in Research Involving Humans, 1999 and as such in accordance with paragraph 2.16, the Chairman was satisfied that the absent member had received all papers and had had an opportunity to have his views recorded and considered.

7. The committee approved amendments 1 and 2 dated 2 Aug 2000 and endorsed the amended Protocol marked "Final Protocol plus amendments 1 and 2" dated 2 Aug 00. Approval to proceed was given in ADMEC letter 1904/2000 dated 22 Aug 2000.

8. Details of the qualifications of the members of the Australian Defence Medical Ethics Committee are enclosed at Annex A.

Yours sincerely,

s22 [redacted]

M. Blenkin
Lieutenant Commander
Executive Secretary
Australian Defence Medical Ethics Committee

4 October, 2000

Annex:
A. Australian Defence Medical Ethics Committee: Qualifications of Members

ANNEX 1
DHSB 2230/2000

Australian Defence Medical Ethics Committee: Qualifications of Members

s47F

DEFENCE PERSONNEL EXECUTIVE
DEFENCE HEALTH SERVICE BRANCH

CP2-7-66 Department of Defence CANBERRA ACT 2600

18

PE 2000/15605/1
ADMEC 216/00
DHSB /957 /2000

Lieutenant Colonel P.E. Nasveld
Senior Medical Officer 7th Brigade
c/- Australian Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

Dear Lieutenant Colonel Nasveld,

AUSTRALIAN DEFENCE MEDICAL ETHICS COMMITTEE (ADMEC) PROTOCOL 216/00: A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR

1. The Committee considered and approved the proposed changes to your protocol at the meeting on 21st August 2000. Please be reminded that your next progress report is due on 30 December 2000.

2. ADMEC requests that in future if amendments to protocols are extensive, changes be displayed using strike through, to clarify their context. Please contact me if you would like to discuss this further.

Yours sincerely,

s22 [redacted]

M. BLENKIN
Lieutenant Commander
Executive Secretary
Australian Defence Medical Ethics Committee

28 August, 2000

A randomized, double-blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor

Protocol Number SB 252263/033
(ADMEC No. 216/00)

PROTOCOL AMENDMENT 2

Final Protocol Approval Date: 18th May 2000

Amendment 2: 2nd August 2000

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1. General

The majority of the changes referred to in this Amendment are the result of review of the protocol by the US Army Medical Research and Materiel Command's (USAMRMC) Human Subjects Research Review Board (HSRRB). They are an established Institutional Review Board (Ethics Committee), but as the subjects involved in this study are not part of, or otherwise associated with the US Army, they would not normally have any influence as far as Ethics Approval of the study is concerned. However, review and approval by the HSRRB is a pre-requisite of budget approval for the study (USAMRMC are co-Sponsors with SB), and thus their approval is essential, and requests by the HSRRB for changes to the protocol should be included wherever possible.

There are two major changes to the protocol that are not the result of HSRRB recommendations.

The first is that the visit schedule for the study is now for visits at 4, 8, 16 and 26 weeks, with a 'window' of +/- 4 weeks for the week 26 visit. This allows for certain subjects being deployed for shorter or longer periods than the majority, and replaces the previous schedule of visits at 4, 8, 16 and 24 weeks with possible additional visits at 28 and 32 weeks. Therefore, throughout the protocol, wherever weeks 24, 28 or 32 are mentioned they have been replaced by week 26 (+/- 4 weeks), and all references to additional visits have been deleted.

The second non-HSRRB change is the inclusion of ECGs on the 100 or so subjects selected for additional phospholipidosis and methaemoglobin assessments. ECGs will be done at screening and at the final prophylaxis visit for these subjects. the rationale for this will be detailed later in this amendment.

Some minor corrections to spelling or grammar may also have bee made. These will not be referred to specifically in this amendment.

2. Study Flow Chart, p.4

This has been updated according to the comments in 1 above regarding visit schedule and addition of ECGs. The footnotes have been altered accordingly.

3. Section 6a, Number of Subjects, p.19

In response to a query from HSRRB, further details on how the subjects to be involved in phospholipidosis, metHb and ECG assessments are to be selected have been included. The second paragraph of this section has been altered as follows:

Was:

Phospholipidosis and methaemoglobin assessments will be performed on a selected sample of approximately 100 subjects.

Is:

Phospholipidosis, methaemoglobin and ECG assessments will be performed on a sample of approximately 100 subjects (one Company of the Battalion). The Company to be selected will be decided according to operational logistics immediately prior to deployment.

3. Section 7a ii, Informed Consent, p.21

In response to HSRRB, the process of obtaining informed consent has been explained in detail. The following paragraph has been added at the end of this section:

Informed consent will be obtained in the following way: 1 month prior to deployment, educational sessions focussing on vector borne disease will be conducted for all troops and units deploying to East Timor with the 1 RAR Battalion Group. The study will be introduced at this stage with briefing in Company sized groups (approximately 100). Potential subjects will be given a copy of the information sheet at this stage. If still interested, they will be asked to register an "expression of interest" and their details will be entered on a screening log. Approximately 2 weeks prior to deployment, those who indicated interest will be further briefed by the Investigators and "Informed Consent" obtained in groups no greater than Platoon size (29 soldiers). The Platoon Commander and Sergeant will be interviewed separately to the remainder of the Platoon to reduce the likelihood of "undue influence". Once formal informed consent has been obtained, subjects will enter the screening phase of the study. The "Ombudsman" role for this study will lie with the Senior Health Officer North Queensland who is not involved in the study but holds responsibility for the delivery and quality of health care in Townsville, from where the volunteers will be selected. The current occupant of this position is LtCol Carmel Van Der Rijt, Clinician and Commanding Officer of Lavarack Barracks Medical Centre (LBMC) which will be providing laboratory and X-ray support to the study.

4. Section 7c i, Collection and preparation of blood samples, p.23

This section has been updated to reflect the reduced total number of blood samples (7 instead of 9), and the consequent reduction in total blood volume required from each subject (63 ml as opposed to 81ml). The final paragraph relating to additional blood samples at weeks 28 and 32 has been deleted.

5. Section 7c ii, Measurement of Parasitaemia, p.24

As dual slide reading is the standard for the phase III programme for tafenoquine, all slides, whether positive or negative for malaria species, must be read by two microscopists. This section has been modified to make this clear. In addition, a paragraph has been added to note

that information on malaria syptoms will also be collected. This section has been amended as follows:

Was:

As parasitaemia is the major endpoint of this study, thick and thin blood films for malaria will be obtained from the venous sample (see (i) above) at screening to exclude malaria at the point of entry. Additional smears* will be performed at scheduled visits and on any day a volunteer presents to a medical facility complaining of fever or experiencing any other clinical signs consistent with malaria. Smears from symptomatic volunteers will be read initially by the treating facility and then forwarded to AMI for confirmation by a microscopist "blinded" to both study treatment and the previous reader's result . Thick and thin blood films will be stained with Giemsa and evaluated by standard techniques. A total of 200 high-power fields will be viewed before a sample is declared negative. Parasite counts will be expressed per 500 white cell count.

Disagreements between the treating facility reading of the slide and AMI will be adjudicated by a third microscopist. If two microscopists agree that the blood smear is positive, then that volunteer will be classified as a failure of prophylaxis.

* Smears will also be performed on any subject who contracts Rickettsia, prior to commencing treatment with doxycycline.

Is:

Thick and thin blood films for malaria diagnosis will be obtained from the venous sample (see (i) above) at screening to exclude malaria at the point of entry. Additional smears* will be performed at scheduled visits and on any day a volunteer presents to a medical facility complaining of fever or experiencing any other clinical signs consistent with malaria. All smears will be read initially by the treating facility and then forwarded to AMI for confirmation by a microscopist "blinded" to both study treatment and the previous reader's result. Thick and thin blood films will be stained with Giemsa and evaluated by standard techniques. A total of 200 high-power fields will be viewed before a sample is declared negative. Parasite counts will be expressed per 500 white cell count.

Disagreements between the treating facility reading of the slide and AMI will be adjudicated by a third microscopist. If two microscopists agree that the blood smear is positive, then that volunteer will be classified as a failure of prophylaxis.

If symptoms of malaria are present at the time of diagnosis of malaria, this will be recorded in the CRF.

* Smears will also be performed on any subject who contracts Rickettsia, prior to commencing treatment with doxycycline.

6. Section 7c iv, Plasma Drug Concentration, p.25

It has been decided that a sample for plasma drug concentration should be collected from all treatment failures in the first 12 weeks of the relapse follow-up phase, so that a correlation can be made between early relapse and plasma drug concentration. Therefore the final paragraph has been amended as follows:

Was:

Note: Two additional blood samples will be taken for measurement of plasma drug concentration from any subject diagnosed with malaria during the study. . The first will be at the time of developing parasitaemia and the second 12 weeks later at the subject's final safety follow-up visit.

Is:

Note: Two additional blood samples will be taken for measurement of plasma drug concentration from any subject diagnosed with malaria during the prophylaxis phase of the study. The first will be at the time of developing parasitaemia and the second 12 weeks later at the subject's final safety follow-up visit. For any subject who develops parasitaemia during the relapse follow-up phase (up to week 12 only) a single sample will be collected at the time of diagnosis.

7. Section 7c v, Assessment of Phopholipidosis (Slit lamp), p.26

Further investigation of the assessment of phospholipidosis has shown that a full eye examination is necessary rather than just the slit lamp. Therefore, this paragraph has been amended as follows:

Was:

Slit lamp:

This examination, which involves immobilising the subject's head by resting his chin on a metal bar, permits a magnified and properly illuminated view of the surface of the eye, eyelids, cornea, retina and associated structures.

The first assessment will be performed at the start of the study before dosing commences and the second at the end of the 6 month prophylactic phase.

Is:

Eye examination:

A slit lamp examination, along with retinal examination and standard tests of visual field and acuity will be performed at the start of the study during screening and at the end of the 6 month prophylactic phase.

The slit lamp examination involves immobilising the subject's head hy resting his chin on a metal bar, and permits a magnified and properly illuminated view of the surface of the eye, eyelids, cornea, retina and associated structures.

8. Section 7c xi, Electrocardiogram, p.28

This is a new section added between 'Pregnancy Testing' and 'Physical Examination'. This has been added in response to a requirement by the CPMP (European Regulators) to collect ECG data on a sample of subjects under study in any studies involving a drug which has shown possible QT interval effects in previous pre-clinical or clinical trials. The following has been added:

An ECG measurement will be performed on the group of 100 subjects involved in phospholipidosis and methaemoglobin assessments during the screening period and at week 26. The exact time of the ECG will be recorded in the CRF for later comparison with the time of most recent administration of study medication.

The ECG measurements are performed as part of the safety assessment for analysis of any possible QT effects.

9. Section 7d ii, Subject Screening (Day –14 to –1), p.28

ECG (selected sample only) added to list of assessments.

10. Section 7d vii, Final Prophylaxis Visit, p.30

This section has been altered to reflect the change to this visit from week 24 (plus possible additional visits at weeks 28 and 32) to week 26 (+/- 4 weeks).

Was:

This visit will occur at week 24 for the majority of subjects. However, for those subjects deployed for more than 6 months due to additional duties, this visit may occur at week 28 or possibly week 32.

At this visit, the following assessments will be performed and details recorded in the CRF.

- blood smear for assessment of parasitaemia
- haematology / biochemistry
- plasma drug concentration (week 24 only)
- adverse events
- concomitant medication
- pregnancy test (females only)
- physical examination
- phospholipidosis assessments (selected sample only)*
- methaemoglobinaemia (selected sample only)*

For each of these visits, a 'window' of ± 2 weeks is allowable.

* These assessments will be performed whilst subjects are in barracks in Australia after return from deployment. They are not likely to be performed at the same time as the other assessments in this visit.

Is:

This visit will occur at week 26 for the majority of subjects. However, due to varied duties, some subjects may be deployed for a shorter or longer period. Therefore, the 'window' for the final prophylaxis visit is 26 +/- 4 weeks.

At this visit, the following assessments will be performed and details recorded in the CRF.

- blood smear for assessment of parasitaemia
- haematology / biochemistry
- plasma drug concentration
- adverse events
- concomitant medication
- pregnancy test (females only)
- physical examination
- phospholipidosis assessments (selected sample only)
- methaemoglobinaemia (selected sample only)
- ECG (selected sample only)

All assessments at this visit will be performed whilst subjects are in barracks in Australia after return from deployment. The phopholipidosis assessments are not likely to be performed at the same time as the other assessments in this visit.

11. Section 7d viii, Week 6 Relapse Follow-up phase, p.31

'Malaria status' has been added as a specific assessment to be recorded in the CRF.

12. Section 7d ix, Week 12 Relapse Follow-up phase, p.31

'Malaria status' has been added as a specific assessment to be recorded in the CRF.

13. Section 8d, packaging, p.33

This section has been amended to indicate that randomisation is stratified, and thus medication numbers will be assigned to subjects according to stratum.

Was:

The medication will be provided in foil blister packs.

Is:

The medication will be provided in foil blister packs. Medication numbers will be allocated to 6 strata (stratified randomisation). There will be 4 strata each with 120 medication numbers, one stratum with 112 medication numbers and 1 stratum with 160 medication numbers.

14. Section 8f, Storage, p.33

The sentence and additional paragraph below have been added at the request of HSRRB:

"The Platoon Sgt has no medical qualifications above first aid training.

Medications will be stored by AMI with only 4 weeks supply at a time being released forward for each volunteer, under the control of the Platoon Sergeant. In Company base areas and Headquarters rear areas this function will be performed by Medics and Regimental Aid Post staff. AMI staff will undertake roving monitoring each week and weekly checks will be conducted for all volunteers by AMI staff.'

15. Section 8g, Drug accountability, p.34

The sentence below has been added at the request of HSRRB:

' Supplies will be inventoried when received and after the closing of the study. Weekly checking fulfils the requirement for drug accountability records to be maintained throughout the study so that there is a perpetual reconciliation of study supplies.'

16. Section 12b, Procedures for handling withdrawals, p.40

Sentence added to the end of the first paragraph at the request of HSRRB:

'Any subject who withdraws due to an AE will be followed until the AE is resolved.'

17. Section 14, Data Evaluation. p.41

This whole section has been updated to reflect the outcome of discussions regarding appropriate analysis and reporting requirements. The decision has been made to make an initial report on the study after 12 weeks of the relapse follow-up phase. In addition, this section now states that an Independent Data Monitoring Committee (IDMC) will be set up so that, should unexpected results be observed (especially high rates of malaria infection) this committee can investigate the possible causes and make decisions on the safety of the study.

Specific changes are summarised below:

a) Section 14a, final paragraph and table

Was:

Assuming 10% of randomised subjects are ineligible for inclusion in the per protocol population results in 426 efficacy evaluable subjects on tafenoquine and 142 on mefloquine. This gives a power of 93% to detect that the upper limit of the two- sided 95% confidence interval for the difference in failure rates (tafenoquine – mefloquine) at the end of the prophylactic phase is no more than 10%, assuming an underlying failure rate of 10% in each treament group. This calculation is based on the formula of Makuch and Simon. The table below shows the sensitivity of this under different assumptions :

Failure Rate per Group	Limit of Non-inferiority	Power
10%	10%	93%
10%	9.5%	90%
10%	7.5%	73%
10%	5%	40%
5%	5%	65%

Is:

With 450 subjects on tafenoquine and 150 on mefloquine in the per protocol population, the study has 94% power to detect that the upper limit of the two- sided 95% confidence interval for the difference in failure rates (tafenoquine – mefloquine) at the end of the prophylactic phase is no more than 10%, assuming an underlying failure rate of 10% in each treatment group. This calculation is based on the formula of Makuch and Simon. The table below shows the sensitivity of this under different assumptions :

Failure	Limit of Non-	Power

Rate per Group	inferiority	
10%	10%	94%
10%	7.5%	75%
10%	5%	42%
5%	5%	68%

b) Section 14c, Breaking the study Blind

Was:

A SB statistician will be responsible for breaking the blind after collection, databasing and cleaning of all data has been completed, and after identification of protocol violators.
Is:

The initial reporting of this study will occur after the first three months of the relapse follow-up phase has been completed for all subjects. All AE data and key efficacy data will have been collected at this time. The only data remaining is information on malaria relapse, collected via telephone, and the investigator will remain blind to treatment at the time of the telephone contact. A SB statistician will be responsible for breaking the blind (once the database is locked) after collection, databasing and cleaning has been completed of all data from the prophylactic phase and first three months of the relapse follow- up.

c) Section 14d i, Endpoints

Was:

Since the primary objective of the study is to assess safety and tolerability of the two treatment regimens, and conclusions regarding the efficacy of the regimens are difficult without knowledge of the placebo attack rate, only the following measures of effectiveness will be assessed:

Prophylaxis Phase:

At the end of the prophylaxis treatment period, the prophylactic outcome for each subject will be derived as follows:

Prophylactic Success: No single positive smear during prophylactic study drug administration up until the end of the prophylaxis treatment period.

Prophylactic Failure: Single positive smear during prophylactic study drug administration up until the end of the prophylaxis treatment period.

Relapse Follow- Up Phase:

At the end of the relapse follow- up phase, the relapse follow- up outcome for each subject will be derived as follows:

Relapse Follow- Up Success: No evidence of malaria in the 6 months after return to Australia

Relapse Follow- Up Failure: Evidence of malaria in the 6 months after return to Australia.

Is:

The primary objective of the study is to assess the safety and tolerability of the two treatment regimens, and conclusions regarding the efficacy of the regimens are difficult without knowledge of the placebo attack rate. However, as a secondary objective is to compare the effectiveness of the two treatments, the following efficacy endpoints will be analysed:

Primary Efficacy Variable:

At the end of the prophylaxis treatment period, the prophylactic outcome for each subject will be derived as follows:

Prophylactic Success: No single positive smear during prophylactic study drug administration (tafenoquine/ mefloquine) up to and including the day of the last dose of eradication medication (placebo/ primaquine).

Prophylactic Failure: Single positive smear during prophylactic study drug administration (tafenoquine/ mefloquine) up to and including the day of the last dose of eradication medication (placebo/ primaquine).

Secondary Efficacy Variables:

The secondary variables are

- number of subjects experiencing malaria at any time during the study
- number of subjects with single positive smear (*P. falciparum* only) during prophylactic study drug administration up to and including the day of the last dose of eradication medication
- number of subjects with single positive smear (*P. vivax* only) during prophylactic study drug administration up to and including the day of the last dose of eradication medication
- time to single positive smear (all species) at any time during the study (prophylactic phase plus 6 months relapse follow- up phase).

Additionally the number of subjects with parasites of species other than *P. falciparum* and *P.vivax*, the number of subjects who test positive at different time points and the number of subjects with symptomatic vs. asymptomatic parasitemia will be summarised.

d) Section 14d ii, Subject Populations

Was:

Two populations are defined for the analysis of clinical efficacy data.

Intent-To- Treat (ITT): All subjects who took at least one dose of study medication and provided at least one smear during the prophylaxis treatment period.

Per Protocol (PP): All randomized subjects who satisfied those inclusion/exclusion criteria with the potential to affect efficacy, and subsequently adhered to the protocol. This is a subset of the ITT population.

Subjects who receive the wrong coded study medication will be analyzed according to the treatment they received.

Subjects will only be excluded from the PP population from the time that the violation occurs. If a subject is a prophylactic failure and then subsequently violates the protocol they will not be excluded from the PP population since they have already satisfied the criteria for failure prior to violation of the protocol.

The ITT population is used to address the question "How does the medication work in subjects who are prescribed the drug and who take at least one dose of the drug?" Subjects will be excluded from the ITT population if there is documented evidence that they have taken no study medication. The PP population is used to address the question "How does the medication work in subjects who are prescribed the medication and who take the medication as prescribed?".
In trials designed to show non- inferiority of a new drug compared to a comparator treatment, the PP population is thought of as a conservative approach to the statistical analysis. For this reason, the PP population is the population of primary interest for the analysis of effectiveness in this study.

All decisions on eligibility for inclusion in these populations will be made prior to code- break or any data evaluation.

Is:

Two populations will be used for the efficacy analysis:

Intent-To- Treat (ITT) : All subjects who took at least one dose of prophylactic study medication during the prophylaxis treatment period.

Per Protocol (PP): All randomised subjects who satisfied those inclusion/exclusion criteria with the potential to affect efficacy and subsequently adhered to the protocol. This is a subset of the ITT population.

Subjects who receive the wrong coded study medication will be analysed according to the treatment they received.

Subjects will only be excluded from the PP population from the time that the violation occurs. If a subject is a prophylactic failure and then subsequently violates the protocol they will not be excluded from the PP population since they have already satisfied the criteria for failure prior to violation of the protocol.

The ITT population is used to address the question "How does the medication work in subjects who are prescribed the drug and who take at least one dose of the drug?" Subjects will be excluded from the ITT population if there is documented evidence that they have taken no study medication. The PP population is used to address the question "How does the medication work in subjects who are prescribed the medication and who take the medication as prescribed?"

In trials designed to show non- inferiority of a new drug compared to a comparator treatment, the PP population may be thought of as a conservative approach to the statistical analysis. For this reason, the PP population is the population of primary interest for the analysis of effectiveness in this study.

All decisions on eligibility for inclusion in the ITT population will be made prior to code-break or any data evaluation.

e) Section 14e ii, Effectiveness Analysis

The title of this section has been changed to 'Primary Efficacy Analysis.'

Was:

Prophylactic outcome and relapse follow- up outcome in each treatment group will be summarised. A comparison of effectiveness in the prophylactic phase will be made by calculating a 95% stratified confidence interval for the difference in the proportion of prophylactic failures (tafenoquine- mefloquine). A conclusion of non- inferiority of tafenoquine will be drawn if the upper limit of this confidence interval is no more than 10%. The confidence interval will be stratified by Company.

Additionally, the proportion of relapse follow- up failures in each treatment group will be analysed. The effectiveness of the two treatments against different malaria species throughout both the prophylactic and the relapse follow- up phase will be summarised.

Is:

The primary objective of the study is to compare the safety and tolerability of the two treatments. However, as a secondary consideration, a comparison of effectiveness in the prophylactic phase will be made by calculating a 95% confidence interval stratified by company for the difference in the proportion of prophylactic failures (tafenoquine-mefloquine). A conclusion of non- inferiority of tafenoquine will be drawn if the upper limit of this confidence interval is no more than 10%.

To confirm the appropriateness of using a stratified confidence interval approach an analysis testing for a treatment by company interaction will be performed.

As confirmation of the primary analysis the above will be repeated for the ITT population, and a covariate analysis will be performed.

f) Section 14e iii, Secondary Efficacy Analysis

This is an additional section:

For the secondary efficacy variables number of subjects with malaria at any time in the study, number of subjects with a single positive smear (P. *falciparum* only) during the prophylactic phase and number of subjects with a single positive smear (*P. vivax* only) during the prophylactic phase, the 95% stratified confidence interval for treatment difference in proportions as described above will be presented. Again, in each case to confirm the appropriateness of using a stratified confidence interval approach an analysis testing for a treatment by company interaction will be performed.

For time to malaria, a Kaplan- Meier curve will be produced showing the cumulative survival rates for each treatment group.

g) Section 14e iv, Interim Analysis

Was:

No interim analyses are planned for this study

Is:

It is planned to set up an independent data monitoring committee (IDMC) to monitor failure rates over the course of the study if required. However no adjustment will be made for multiple comparisons.

The initial reporting of this study will occur at the end of the first twelve weeks of the relapse follow- up phase, with the remaining data on malaria relapse in the last three months being reported at a subsequent timepoint, since all subjects will be analysed at the end of the relapse follow- up phase. However this is not a formal interim analysis and consequently no adjustment of the alpha level will be made.

h) Section 14f, Planned Safety Evaluation

The 5th paragraph has been changed.

Was:

For frequently occurring AEs (≥ 5% subjects in either treatment group) the proportion of subjects reporting the AE will be compared between treatments using Fisher's exact test, and two-sided 95% confidence intervals will be used to estimate the difference in proportions between treatment groups.

Is:

For frequently occurring AEs (≥ 5% or 10% subjects in either treatment group - to be decided according to the number of AEs occurring at these levels) the proportion of subjects reporting the AE will be compared between treatments using Fisher's exact test, and two-sided 95% confidence intervals will be used to estimate the difference in proportions between treatment groups.

18. Appendix B, Information Sheet, p.54

A number of changes have been made to the Information Sheet and Consent Form, by request of HSRRB. These include that page numbers have been added to each page of the Information Sheet, the subject's address has been added and spaces for subject and witness initials have been added to each page. A space for the Witness' signature has been added to the Consent Form. Other changes resulting from HSRRB review are detailed below. The only change not related to HSRRB is the addition of information on ECGs.

a) Purpose / Benefits of the Study

The wording of the first paragraph has been slightly changed. The Title has been changed to 'Purpose of the Study'. 'Benefits' has been moved to a separate section.

Was:

Because you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this

potentially life-threatening disease. The purpose of this study is to look at how effective a new drug, ***tafenoquine*** is in preventing malaria. We also wish to compare tafenoquine with another drug, ***mefloquine***, which has been widely used over the past decade and is one of the alternative drugs currently used by the ADF to prevent malaria.

The benefit of taking part in the study is that you will be more closely monitored for the development of malaria during and after your deployment. You will be taking a medication once weekly rather than once daily with the ADF standard drug, doxycycline. In addition, the study results may provide a better understanding on how to prevent malaria infection on future overseas deployments.

Is:

Because you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. The purpose of this study is to look at the safety and effectiveness of a new drug, ***tafenoquine***, for the prevention of malaria. We also wish to compare tafenoquine with another drug, ***mefloquine***, which has been widely used over the past decade and is one of the alternative drugs currently used by the ADF to prevent malaria.

b) What is the Medicine?

An additional paragraph has been added after the second paragraph relating to primaquine eradication medication.

Was:

If you agree to take part in the study, you will be assigned at random to one of two treatment groups. The study will be "***double-blinded***" which means that neither you nor your doctor will be aware which medication you are taking.

You will receive either one tafenoquine (200mg) capsule each day for three consecutive days during pre-deployment training followed by one tafenoquine capsule weekly throughout the deployment or one mefloquine (250mg) capsule each day for three consecutive days during pre-deployment training followed by one mefloquine capsule weekly throughout the deployment. You will have a 75% chance of being on tafenoquine and a 25% chance of being on mefloquine. You will take all medication with food to reduce side effects. The doses will be issued to you weekly so we can accurately record when you have taken your medication.

While tafenoquine has been given to several thousand individuals safely (including more than 1,000 ADF personnel during trials in Bougainville and East Timor), it has not yet been registered with the regulatory authorities in Australia. Consequently it is still defined as an "experimental" compound.

Is:

If you agree to take part in the study, you will be assigned at random to one of two treatment groups. The study will be "*double-blinded*" which means that neither you nor your doctor will be aware which medication you are taking.

You will receive either one tafenoquine (200mg) capsule each day for three consecutive days during pre-deployment training followed by one tafenoquine capsule weekly throughout the deployment or one mefloquine (250mg) capsule each day for three consecutive days during pre-deployment training followed by one mefloquine capsule weekly throughout the deployment. You will have a 75% chance of being on tafenoquine and a 25% chance of being on mefloquine. You will take all medication with food to reduce side effects. The doses will be issued to you weekly so we can accurately record when you have taken your medication.

When you return to Australia, you will undergo treatment to get rid of any malaria parasites that may have collected in your liver. Those who received mefloquine will be given the standard drug used for this purpose called primaquine. You will take one capsule (15mg) twice a day for 14 days. If you received tafenoquine, this eradication course is not necessary, therefore you will take one capsule of placebo twice a day for 14 days. As before, you will not know which treatment you are taking, but you will have a 75% chance of receiving placebo and a 25% chance of receiving primaquine.

While tafenoquine has been given to several thousand individuals safely (including more than 1,000 ADF personnel during trials in Bougainville and East Timor), it has not yet been registered with the regulatory authorities in Australia or the USA. Consequently it is still defined as an "experimental" compound.

c) Study Tests

Paragraph 2 altered to include ECG:

Was:

A selected Company sized group will also have additional tests (including chest X-ray) done to look at other effects that either of the study drugs may have, as well as.....

Is:

A selected Company sized group will also have additional tests (including chest X-ray and ECG) done to look at other effects that either of the study drugs may have, as well as.....

d) Risks / Discomforts

A sentence on risks of primaquine has been added. An additional paragraph has been added warning that it is possible that a subject could catch malaria whilst on the study even though they are taking prophylactic medication.

Was:

..... with depression and anxiety. Both tafenoquine and mefloquine are considered to be safe, however, neither is recommended for use in pregnant females.

Is:

..... with depression and anxiety. Both tafenoquine and mefloquine are considered to be safe, however, neither are recommended for use in pregnant females. Primaquine has similar side-effects to tafenoquine including the risk of producing the bleeding disorder related to a lack of G6PD, as described above.

Although you will be taking study medication designed to prevent malaria, there is a very small chance that you may contract malaria while on the study. However, if you do contract malaria you will be treated by your company medic or study investigator and followed up until you are better.

e) Benefits

This is a new section that has been added (cut from original Purpose / Benefits of the Study – see a above).

The benefit of taking part in the study is that you will be more closely monitored for the development of malaria during and after your deployment. You will be taking a medication once weekly rather than once daily with the ADF standard drug, doxycycline. In addition, the study results may provide a better understanding on how to prevent malaria infection on future overseas deployments.

f) Precautions, Contraception

The following sentence has been added:

It should be remembered that no barrier or pharmaceutical method of contraception is 100% effective.

g) Confidentiality

Was:

In all reports only a study number will identify you. The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

s47f

From time to time a monitor representing the sponsors of the study (SmithKline Beecham), or a regulatory authority such as the Therapeutic Goods Administration in Australia, may require access to your medical records to ensure that the study is being carried out to the international standards under Good Clinical Practice (GCP). This access will be supervised by one of the study team and all monitors are bound by a confidentiality agreement.

Is:

In all reports, publications or presentations about this research, information about you and your participation in this study will be kept in the strictest confidence and will not be released in any form that personally identifies you (a study number only will be used). The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

From time to time a monitor representing the sponsors of the study (SmithKline Beecham / US Army Medical Research and Materiel Command), or a regulatory authority such as the Therapeutic Goods Administration in Australia or the US Food and Drug Administration, may require access to your medical records to ensure that the study is being carried out to the international standards under Good Clinical Practice (GCP). This access will be supervised by one of the study team and all monitors are bound by a confidentiality agreement.

It is the policy of the USAMRMC that data sheets are to be completed on all volunteers participating in research for entry into the Command's Volunteer Registry Database. This is a confidential database and the data entered include name, address, social security number (or equivalent) and details of the clinical trial. This information is needed to answer questions concerning subjects participating in research sponsored by USAMRMC, and to ensure that subjects can be contacted if there is new information on the study drug. The information will be stored for 75 years.

k) Compensation

Was:

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. Should you consider injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest

medical facility. The study investigators may be advised by calling the pager number on your study ID card.

Is:

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. Compensation other than medical care will be provided according to the compensation provided as a member of the Australian Army. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study. Should you consider injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility. The study investigators may be advised by calling the pager number on your study ID card.

i) Informed Written Consent

The following phrase has been removed from the first sentence:
'..... and understand all the points addressed.'

19. Appendices C and D

These have been swapped round so that 'Pharmacokinetic Sampling' is now Appendix C and 'References' is now Appendix D.

A randomized, double-blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor

Protocol Number SB 252263/033
(ADMEC No. 216/00)

PROTOCOL AMENDMENT 1

Final Protocol Approval Date: 18th May 2000

Amendment 1: 22nd June 2000

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1. General

This amendment deals with a number of alterations to the protocol, some of which are just minor typographical errors. These errors will not be referred to specifically in this amendment.

A brief rationale for each change is included only if the change does not speak for itself.

2. Title page

Name of Medical Monitor (Capt Kym Ward, Regimental Medical Officer, 1 RAR) added to list of Investigators.

s47F [redacted] (SB Medical Monitor) added to list of sponsor contact names.

3. Study flow chart, page 4

Window for screening visit was days –7 to –1, now changed to –14 to –1.

Blood smear for parasitaemia added at screening visit.

4. Section 2 c i, page 10

Title of this section renamed "Pre-Clinical Pharmacology, Toxicology and Pharmacokinetics."

5. Section 2 c ii and iii, page 10

Sections ii (Efficacy) and iii (Toxicology) removed and reference made to data in the Investigator Brochure.

6. Section 4, Objectives, page 17

Objectives split into Primary and Secondary Objectives.

7. Section 7 a, Ethics and Regulatory Considerations, page 20

Was:

The protocol will be submitted for appraisal and approval by the Australian Defence Medical Ethics Committee (ADMEC). Regulatory approval will be obtained as necessary from the Therapeutic Goods Administration (TGA) in Australia and other regulatory bodies if required.

Is:

The protocol will be submitted for appraisal and approval by the Australian Defence Medical Ethics Committee (ADMEC). Regulatory approval (Clinical Trial Notification) will be obtained from the Therapeutic Goods Administration (TGA) in Australia.. Approval will also be obtained from the US Army Human Subject Research Review Board (HSRRB).

8. Section 7 c i, Collection and Preparation of blood samples

A change to the wording of the final paragraph has been made in order to clarify the procedure for collection of samples for analysis of plasma drug concentration.

Was:

Bleeding Schedule

All volunteers will be bled on a predetermined day of the assessment weeks following their dose of tafenoquine or mefloquine. Pre-determined days will be day one, three, five or seven after tafenoquine or mefloquine.

Is:

Bleeding Schedule (all blood samples):

To allow for the analysis of population pharmacokinetics (PK), blood samples will be collected from all study subjects on pre-determined days after dosing on each of the assessment weeks. The pre-determined days will include day 1 (early post-dose, absorption phase), days 3 and 5 (72 – 120 hours post-dose), and day 7 (pre-dose, trough plasma level). Therefore, for example, at week 4, one Company will be bled on day 1, one on day 3, one on day 5 and one on day 7. Thereafter, Companies will be bled in a cyclical fashion such that, at the end of the study, each Company will have been bled on at least one occasion on day 1, 3, 5, or 7. However, the sample on Day 2 of the study (1 – 12 hours post-final loading dose) will be collected from all study subjects. For further details refer to Appendix D.

9. Section 7 c iv, Plasma Drug Concentration, page 25

The wording of this paragraph was changed in order to clarify the procedure.

Was:

During the course of the study, measurements of plasma drug concentration will be made at or around the times of scheduled visits in order to characterise the population pharmacokinetics of tafenoquine in a subset of study subjects. For full details, please refer to Appendix D. (Plasma for these measurements will come from the samples collected for haematology).

An additional blood sample will be taken from any subject diagnosed with malaria during the study for measurement of plasma drug concentration by AMI and SB.

10. Section 7 c v, Assessment of Phospholipidosis, page 26

The wording of the final paragraph of this section has been changed to indicate that FEV_1 and chest X-ray must be performed before both D_LCO measurements, i.e at the start and end of the prophylactic phase.

Was:

NOTE: To exclude pre-existing abnormalities, a chest X-ray* and FEV_1 test must be performed *prior to the first measurement of* D_LCO.
*X-ray only required if the subject has not had one in the 4 weeks before study entry.

Is:

NOTE: To exclude pre-existing abnormalities, a chest X-ray* and FEV_1 test must be performed prior to the first and second measurements of D_LCO.
*X-ray at study start only required if the subject has not had one in the 4 weeks before study entry.

11. Section 7 c x, Pregnancy Testing, page 29

This section has been altered to confirm the fact that pregnancy testing is not done on a monthly basis, but at the scheduled study visits (weeks 4, 8, 16 and 24). It has also been updated to demonstrate that additional visits (and hence additional pregnancy tests) may be necessary for some subjects.

Was:

All female subjects with child-bearing potential will be tested for pregnancy at screening and on monthly reviews by blood testing techniques using standard test kits. Women who believe they have become pregnant or who record a positive result on blood testing will be excluded from the study. (see also section 9(g)).

Is:

All female subjects with childbearing potential will be tested for pregnancy at screening and at weeks 4, 8, 16 and 24 * by blood testing techniques using standard test kits. Women who believe they have become pregnant or who record a positive result on blood testing will be excluded from the study. (see also section 11(g)).

* Additional tests will be performed at week 28 and/or week 32 for those subjects deployed to East Timor for more than 6 months.

12. Section 7 d ii, Subject Screening, page 29

The window for this visit has been extended from 7 (days -7 to -1) to 14 (day -14 to -1) days.

In addition, the final sentence of this section has been amended:

Was:

If this sample is taken more than 10 days prior to Day 0, an additional baseline sample must be taken for study purposes.

Is:

<u>If this sample is taken more than 14 days prior to Day 0, an additional baseline sample must be taken for study purposes.</u>

13. Section 7 d v, Day 2, page 30

This section has been amended to reflect agreed changes to the time of collection of blood samples for plasma drug concentration and to clarify the study medication dosing schedule.

Was:

This is the last day of the loading dose regimen.

The following assessments will be performed and details recorded in the CRF.

- adverse events
- concomitant medication
- haematology / biochemistry
- blood sample for assessment of peak plasma drug concentration*

* Sample to be taken 12 hours (range 10 – 14 hours) after last dose of loading regimen. This sample may be part of the sample for haematology and biochemistry.

Is:

This is the last day of the loading dose regimen.

The following assessments will be performed and details recorded in the CRF.

- adverse events
- concomitant medication
- haematology / biochemistry
- blood sample for assessment of peak plasma drug concentration*

* Sample to be taken up to 12 hours (range 1 – 12 hours) after last dose of the loading regimen. Plasma for this assay will be taken from the EDTA sample collected for haematology.

After the final dose of the loading dose is taken, the next dose of study medication will be scheduled for day 7 after the first dose of the loading dose regimen. Thereafter, prophylactic medication will be dispensed to subjects on a weekly basis.

14. Section 7 d vi, Weeks 4, 8 and 16, page 31

'Plasma drug concentration' has been added to the list of assessments at these visits (it had previously been omitted in error).

15. Section 7 d vii, Final Prophylaxis Visit, page 31

As in m) above, 'plasma drug concentration' added to list of assessments.

16. Section 7 d viii, Week 6 Relapse Follow-up phase, page 32

The following sentence has been added to the end of this section. This had been omitted in error:

Any subjects who have symptoms of malaria or who have been diagnosed with malaria will have blood smears taken (see section 7c, General Instructions, page 20). Full details will be recorded in the CRF.

17. Section 7 d ix, Week 12 Relapse Follow-up phase, page 32

The following sentence has been added to the end of this section. This had been omitted in error:

Any subjects who have symptoms of malaria or who have been diagnosed with malaria will have blood smears taken (see section 7c, General Instructions, page 20). Full details will be recorded in the CRF.

18. Section 8, Study Medication and Administration, page 33

This section has had some minor alterations to spelling and grammar. The change of note is that study medication will be provided in blister packs only, not bottles. This section has been amended to reflect this.

19. Section 11 e, Serious Adverse Experiences, page 38

The section 'Reporting Serious Adverse Experiences' has been updated to make the required reporting procedures clear, and to specify the relevant contact details.

Was:

Reporting Serious Adverse Experiences

Any serious adverse experiences which occur at any time during the clinical study or within 12 weeks of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator to the SB contact detailed below by telephone within 24 hours.

Name: *To be advised*

Telephone: *To be advised*

Emergency Number: *To be advised*

Investigators should not wait to receive additional information to fully document the event before notifying SmithKline Beecham of a serious adverse experience. The telephone report should be followed by a full written summary utilising the SB serious AE worksheet detailing relevant aspects of the adverse experiences in question. Where applicable, information from relevant hospital case records and autopsy reports should be obtained.

Instances of death, cancer or congenital abnormality if brought to the attention of the Investigator AT ANY TIME after cessation of study medication AND considered by the Investigator to be possibly related to study medication, should be reported to the Site Monitor.

The Executive Secretary of the Australian Defence Medical Ethics Committee (ADMEC) must be kept informed of all SAEs which occur during the study.

Is:

Reporting Serious Adverse Experiences:

Any serious adverse experiences which occur at any time during the clinical study or within 12 weeks of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator to the SB Medical Monitor (details below) by facsimile, the preferred method of reporting, or by telephone within 24 hours.

s47F

[redacted]

In addition, serious and unexpected adverse experiences must be immediately reported by telephone (and followed up by fax) to:

U.S. Army Medical Research and Materiel Command (USAMRMC)
Deputy Chief of Staff for Regulatory Compliance and Quality
ATTN: MCMR-RCQ,
504 Scott Street,
Fort Detrick,
Maryland 21702-5012.

A written report must follow the initial telephone call within 3 working days and information on the resolution when available. The written report must be addressed to USAMRMC as detailed above.

The Executive Secretary of the Australian Defence Medical Ethics Committee (ADMEC) must be kept informed of all SAEs which occur during the study. Contact details as follows:

Executive Secretary ADMEC
SO1 Medical Standards
DHSB
CP2-7-66

Investigators should not wait to receive additional information to fully document the event before notifying SB, USAMRMC and ADMEC of a serious adverse

experience. The SAE form, which should be completed as fully as possible, or the telephone report, should be followed up with a full written summary utilising the SB SAE worksheet detailing relevant aspects of the serious adverse experiences in question. Where applicable, information from relevant hospital case records and autopsy reports should be obtained.

Instances of death, cancer or congenital abnormality if brought to the attention of the Investigator AT ANY TIME after cessation of study medication AND considered by the Investigator to be possibly related to study medication, should be reported to SB and communicated to USAMRMC and ADMEC.

20. Section 11 g, Pregnancy, page 39

The decision has been made that pregnancies should be reported as SAEs. This section has been updated to reflect this.

Was:

Subjects who become pregnant during the study should discontinue the study immediately.

Subjects should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within 12 weeks of completing their course of study medication.

Whenever possible a pregnancy should be followed to term, any premature terminations reported, and the status of the mother and child should be reported to SmithKline Beecham after delivery.

Is:

Subjects who become pregnant during the study should discontinue the study immediately.

Subjects should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within 12 weeks of completing their course of study medication. Such pregnancies should be reported as an SAE to the SB Medical Monitor.

Whenever possible a pregnancy should be followed to term, any premature terminations reported, and the status of the mother and child should be reported to SmithKline Beecham after delivery.

Please see also section 13.

21. Section 14 d i, Endpoints, page 43

The definition of prophylactic failure and success have been amended as follows:

Was:
Prophylactic Success: No first positive smear during prophylactic study drug administration up until the end of the prophylaxis treatment period.

Prophylactic Failure: First positive smear during prophylactic study drug administration up until the end of the prophylaxis treatment period.

Is:

Prophylactic Success: No single positive smear during prophylactic study drug administration up until the end of the prophylaxis treatment period.

Prophylactic Failure: Single positive smear during prophylactic study drug administration up until the end of the prophylaxis treatment period.

22. Section 14 g, Pharmacokinetic Analysis, page 45

Mefloquine analysis is now to be performed by AMI, Brisbane. This section has been amended accordingly. The followingsentence has been added to the end of this section:

Drug and population pharmacokinetic analysis of mefloquine will be the responsibility of the Australian Army Malaria Institute, Brisbane.

23. Section 15, Administrative Matters, page 45

Throughout this section, where 'SB' is mentioned, this has been replaced by 'SB / USAMRMC' to indicate that both organisations are acting as Sponsor, and that monitoring is their shared responsibility.

24. Section 15 e, Monitoring by SmithKline Beecham, page 47

Changes made to indicate the monitoring requirements of USAMRMC.

Was:

Monitoring visits by a professional representative of the sponsor will be scheduled to take place before entry of the first subject, during the study at appropriate intervals and after the last subject is completed.

These visits are for the purpose of confirming that SB sponsored studies are being conducted in compliance with the relevant Good Clinical Practice regulations/ guidelines, verifying adherence to the protocol and the completeness and exactness of data entered on the CRF and Drug Inventory Forms. The monitor will verify CRF entries by comparing them with the hospital/clinic/office records which will be made available for this purpose. The monitor will retrieve

completed CRF sections at each visit. Adequate time and space for these visits must be made available by the investigator.

The investigator must ensure provision of reasonable space and adequate qualified personnel for monitoring visits.

Is:

Monitoring visits by a professional representative of the sponsor will be scheduled to take place before entry of the first subject, during the study at appropriate intervals and after the last subject is completed.

Monitoring responsibilities for this protocol will be performed by USAMRMC's Quality Assurance Office and SmithKline Beecham. A Pre-Study/Initiation visit will be conducted with monitors from USAMRMC and SmithKline Beecham. A minimum of two periodic monitoring visits will be conducted. At least one of these visits will be conducted by USAMRMC's Quality Assurance Office and the rest will be conducted by monitors from SmithKline Beecham. The Close-Out monitoring visit will be conducted by monitors from both USAMRMC's Quality Assurance Office and SmithKline Beecham. Monitoring Reports will be provided to USAMRMC's Quality Assurance Office and SmithKline Beecham after each monitoring visit.

These visits are for the purpose of confirming that studies are being conducted in compliance with the relevant Good Clinical Practice regulations/ guidelines, verifying adherence to the protocol and the completeness and exactness of data entered on the CRF and Drug Inventory Forms. The monitor will verify CRF entries by comparing them with the hospital/clinic/office records which will be made available for this purpose. The monitor will retrieve completed CRF sections at each visit. Adequate time and space for these visits must be made available by the investigator.

The investigator must ensure provision of reasonable space and adequate qualified personnel for monitoring visits.

24. Section 15 f, Archiving, page 47

The following paragraph has been added to this section, as a requirement of the USAMRMC's Human Subjects Research Review Board (HSRRB).

It is the policy of the U.S Army Medical Research and Materiel Command (USAMRMC) that data sheets are to be completed on all volunteers participating in research for entry into the Command's Volunteer Registry Database. This is a confidential database and the data entered include name, address, social security number (or equivalent) and details of the clinical trial. This information is needed to answer questions concerning subjects participating in research sponsored by USAMRMC, and to ensure that subjects can be contacted if there is new information on the study drug. The information should be stored for 75 years.

25. Information Sheet, 'Study Tests', page 55

The second paragraph of this section has been amended to indicate to the subject that a chest X-ray may be necessary if the subject is one of the group selected for additional measurements.

Was:

A selected Company sized group will also have additional tests done to look at other effects that either of the study drugs may have, as well as having eye and lung function tests done before and after the deployment. This will require an additional 20 mls of blood to be taken.

Is:

A selected Company sized group will also have additional tests (including chest X-ray) done to look at other effects that either of the study drugs may have, as well as having eye and lung function tests done before and after the deployment. This will require an additional 20 mls of blood to be taken.

26. Information Sheet, 'Your rights', page 57

The address of ADMEC has changed:

Was:

Executive Secretary
Australian Defence Medical Advisory Committee
CP-6-45
Department of Defence
Canberra, ACT, 2600

Is:

Executive Secretary
Australian Defence Medical Ethics Committee
CP2-7-66
Department of Defence
Canberra, ACT, 2600

27. Appendix D, Pharmacokinetic Sampling, page 61

This appendix has been amended to clarify the sampling schedule for PK blood samples, and to indicate that AMI, Brisbane will be responsible for the plasma drug concentration analysis for mefloquine.

The first section has been amended as follows:

Was:

Sample Collection

Blood samples will be collected from subjects for pharmacokinetic analysis during the double blind phase, and should include the time points detailed in the table below. These samples may be limited to selected companies of troops. Three post-dose samples will be collected within varying time windows, likely to be: 6-12 hours following administration of the third loading dose, 2-5 hours post-dose on week 8, and 72-120 hours (3-5 days) post-dose week 16. Two additional trough samples may be collected just prior to dosing of study medication on weeks 4 and 24 of the prophylactic phase of the study. It should be possible to adjust the timing of blood draws for safety to fit in with the PK samples.

Post third loading dose (6-12 h)	**Wk 4 pre-dose**	**Wk 8 2-5 h post dose**	**Wk 16 3-5 days post-dose**	**Wk 24 pre-dose**
X	X	X	X	X

In addition, two samples will be collected from each subject who develops parasitemia. One at the time of developing parasitemia, and the second at the week 12 follow-up visit.

No. Patients	**Time of parasitemia**	**Week 12 follow-up**
Any with parasitemia	X	X

If possible, sampling times within a particular window should be spread across that window rather than being grouped at extreme ends of the window (e.g. 6-12 h window - not all samples at 6 h). The **date** and **exact** time of each sample should be recorded on the CRF. The **exact** date and time of administration of the dose prior to the sample collection must also be recorded in the CRF (note: for the loading dose regimen, the exact date and time of all 3 doses should be recorded.

Is:

Sample Collection

Blood samples will be collected from subjects for pharmacokinetic analysis during the double blind phase, and should include the time points detailed in the table below. These samples may be limited to selected companies of troops. Three post-dose samples will be collected within varying time windows, as follows: 1-12 hours following administration of the third loading dose, 1 – 12 - hours post-dose , and 72-120 hours (3-5 days) post-dose.. In addition, trough samples will be collected prior to dosing of study medication. The timing of blood draws for safety will be adjusted to fit in with PK sampling.

Although the logistics of drawing blood from large numbers of subjects in the study environment may not allow, the proposed sampling schedule is as follows (to allow for data from this study to be combined with data from other studies in the phase III programme)

Post third loading dose (1-12 h)	**Wk 4 pre-dose**	**Wk 8 1-12 h post dose**	**Wk 16 3-5 days post-dose**	**Wk 24 pre-dose**
X	X	X	X	X

However, samples will be collected from all subjects at the specified times above relative to dosing, but not necessarily on the assessment weeks specified above (see section 7(c)(i), 'Bleeding Schedule(all blood samples)').

In addition, two samples will be collected from each subject who develops parasitaemia: one at the time of developing parasitaemia, and the second 12 weeks later.

No. Patients	**Time of parasitemia**	**Week 12 follow-up**
Any with parasitemia	X	X

If possible, sampling times within a particular window should be spread across that window rather than being grouped at extreme ends of the window (e.g. 1-12 h window - not all samples at 6 h). The date and exact time of each sample should be recorded on the CRF. The exact date and time of administration of the dose prior to the sample collection must also be recorded in the CRF (note: for the loading dose regimen, the exact date and time of all 3 doses should be recorded).

The following sentence has been added to the end of the final section entitled 'Pharmacokinetic Analysis':

Drug and population pharmacokinetic analysis of mefloquine samples will be the responsibility of the Australian Army Malaria Institute, Brisbane.

DEFENCE PERSONNEL EXECUTIVE
DEFENCE HEALTH SERVICE BRANCH

CP2-7-66 Department of Defence CANBERRA ACT 2600

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PE 2000/15605/1
ADMEC 216/00
DHSB 1326/2000

Lieutenant Colonel P.E. Nasveld
Senior Medical Officer 7th Brigade
c/- Australian Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

Dear Lieutenant Colonel Nasveld

AUSTRALIAN DEFENCE MEDICAL ETHICS COMMITTEE (ADMEC) PROTOCOL 216/00: A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR

1. Thank you for providing the requested amendments to your protocol. ADMEC has now cleared your project to proceed. Please note that ethical clearance from ADMEC does not automatically confer access to ADF personnel; this will have to be sought from the relevant military commanders.

2. Your protocol has been allocated ADMEC Protocol Number 216/00, and this number should be quoted in all correspondence. Six-monthly progress reports are required, the first being due on 30 December 2000. ADMEC's compliance with the NHMRC National Statement on Ethical Conduct in Research Involving Humans requires that your progress reports include, where applicable, comment on: the security of your records; compliance with the approved consent procedures and documentation, and compliance with any other special conditions that ADMEC may have required.

3. For completeness, would you please sign the enclosed researcher's agreement and return it to me at your convenience. I have also enclosed ADMEC's Guidelines for Volunteers, a copy of which is to be given to each study participant. As this is a clinical trial, ADMEC requires that a list of participants be provided once available.

4. The Committee wishes you well with your research. Please contact me if I can be of any assistance.

Yours sincerely,

s22 [redacted]

V.R. ROSS
Lieutenant Colonel
Executive Secretary
Australian Defence Medical Ethics Committee

14 June, 2000

8

ADMEC 2.16.00

Ross, Victoria
To:
Subject: SEC: Unclassified. RE: UNCLASSIFIED:-Consent Form [Clean-Virus Free]

Yes, go ahead, formal approval will be faxed this pm and hard copy to follow.

Vicki

---Original Message---
From:
Sent: Wednesday, 14 June 2000 12:00
To: Ross, Victoria
Subject: SEC: UNCLASSIFIED:-Consent Form [Clean-Virus Free]

<< File: Mac Word 3.0 >>

Vicki,
This was picked up last night by the SKB protocol team and has been corrected.
s47F [redacted]
Find corrected version attached.
Now can I have my clearance and researchers agreement.(See attached file: Consent.doc)
Pete

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APPENDIX B

INFORMATION SHEET

A randomised, double-blind comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor

Principal Investigators:
LtCol Peter Nasveld, MBBS, BScMED, FACRRM
LtCol Mike Edstein, PhD

Protocol No.
SK 252263/033

You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE / BENEFITS OF THE STUDY

Because you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. The purpose of this study is to look at how effective a new drug, ***tafenoquine*** is in preventing malaria. We also wish to compare tafenoquine with another drug, ***mefloquine***, which has been widely used over the past decade and is one of the alternative drugs currently used by the ADF to prevent malaria.

The benefit of taking part in the study is that you will be more closely monitored for the development of malaria during and after your deployment. You will be taking a medication once weekly rather than once daily with the ADF standard drug, doxycycline. In addition, the study results may provide a better understanding on how to prevent malaria infection on future overseas deployments.

WHAT IS THE MEDICINE?

If you agree to take part in the study, you will be assigned at random to one of two treatment groups. The study will be "*double-blinded*" which means that neither you nor your doctor will be aware which medication you are taking.

You will receive either one tafenoquine (200mg) capsule each day for three consecutive days during pre-deployment training followed by one tafenoquine capsule weekly throughout the deployment or one mefloquine (250mg) capsule each day for three consecutive days during pre-deployment training followed by one mefloquine capsule weekly throughout the deployment. You will have a 75% chance of being on tafenoquine and a 25% chance of being on mefloquine. You will take all medication with food to reduce side effects. The doses will be issued to you weekly so we can accurately record when you have taken your medication.

While tafenoquine has been given to several thousand individuals safely (including more than 1,000 ADF personnel during trials in Bougainville and East Timor), it has not yet been registered with the regulatory authorities in Australia. Consequently it is still defined as an "experimental" compound.

WHAT IS THE STUDY?

The study involves up to 700 volunteers receiving tafenoquine or mefloquine weekly throughout the deployment. Should you develop a fever within 12 months of returning home, you are asked to attend your local health facility and show them your study ID card. This ID card will contain details on how you should be investigated, how to contact the investigators, and how you should be treated if malaria is diagnosed.

LENGTH OF THE STUDY

The study will begin during pre-deployment training in Townsville, continue during the deployment, with follow-up until 6 months after your deployment is completed. Your only involvement after redeployment will be normal follow-up (after 6 and 12 weeks) by your RAP according to LHQ directives, plus telephone interviews at 18 and 24 weeks after returning to Australia. Should you get malaria after this, your Doctor or RAP will undertake normal reporting to AMI. There are no additional blood tests during the follow-up period over those normally required for personnel re-deploying from overseas service.

STUDY TESTS

As the investigators are looking at baseline drug levels in your blood, checking your blood for malaria and measuring biochemical (liver and kidney function) and haematological (blood cell) levels in your blood to monitor safety, you will be requested to provide samples of blood from your arm. These tests involve the drawing of 9mls (two teaspoons) of blood on up to 9 occasions. Three (3) of these samples would be required anyway as part of your deployment requirements as directed by LHQ. Over the course of the study, a total of 81mls of blood will be collected.

A selected Company sized group will also have additional tests done to look at other effects that either of the study drugs may have, as well as having eye and lung function tests done before and after the deployment. This will require an additional 20 mls of blood to be taken.

Female volunteers will have pregnancy testing performed on their blood samples on all occasions that blood is taken. No additional blood will be taken for this purpose.

RISKS / DISCOMFORTS

There may be some bruising with blood taken from the veins in your arm.

Tafenoquine has a risk of producing a bleeding disorder if given to people who lack a particular enzyme called G6PD. You have been tested for this enzyme prior to deployment, and will not receive either drug if you have this deficiency. In eight previous clinical trials involving human subjects, including studies in ADF personnel

on Bougainville, tafenoquine was noted to produce nausea, vomiting and diarrhoea in some subjects (usually self limiting and improved by taking the medication with food) and mild headache. Similar side effects are seen with mefloquine. In addition, mefloquine has also rarely (about 1:10,000) been associated with depression and anxiety Both tafenoquine and mefloquine are considered to be safe, however, neither are recommended for use in pregnant females.

PRECAUTIONS

If you have had a significant response to any medications in the past, or have experienced urticaria (hives) or anaphylaxis (a significant allergic reaction involving collapse, swelling of the face and mouth, difficulty breathing) you may not be able to take part in the study. If you have experienced this type of reaction, please discuss this with the study Medical Officer.

Pregnancy - If you think (females only) that you may be pregnant or intend to become pregnant within one month of returning to Australia, please discuss this with the study Medical Officer. It is recommended not to become pregnant within 3 months of ceasing the medication.

Contraception – While taking this medication, it is recommended that females use an accepted form of contraception, which may include abstaining, barrier methods or pharmaceutical methods ("the pill"). Tafenoquine and mefloquine are not considered to interact with Oral Contraceptive Pills. If you are concerned about such interactions or have any questions about contraception while on the medication, please discuss this with the study Medical Officer. Continue precautions for 3 months after stopping treatment.

CONFIDENTIALITY

In all reports only a study number will identify you. The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

From time to time a monitor representing the sponsors of the study (SmithKlein Beecham), or a regulatory authority such as the Therapeutic Goods Administration in Australia, may require access to your medical records to ensure that the study is being carried out to the international standards under Good Clinical Practice (GCP). This access will be supervised by one of the study team and all monitors are bound by a confidentiality agreement.

COMPENSATION

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. Should you consider injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility. The study investigators may be advised by calling the pager number on your study ID card.

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the study investigators, or your medical facility. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP2-7-66
Department of Defence
Canberra, ACT, 2600
Phone: (02) 6266 3925

INVESTIGATOR RESPONSIBILITIES

The investigators are responsible for ensuring that the study is conducted according to accepted Good Clinical Practice (GCP) standards, and for ensuring that the well being of study participants is always considered over all other considerations. Additionally, they are required to advise you in a timely manner should any other information become available that may be relevant to your willingness to participate in the study.

YOUR RESPONSIBILITIES

Should you agree to enter the study, you should be prepared to undertake all doses of drug required during the deployment, as well as all tests and follow-up required. Should you experience any medical problems, including suspected side effects to the study drugs, you should report these promptly to your Coy medic, RAP or study investigator. If you want any further information on the study, please contact the study investigator named on the attached consent form.

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled.. Should you choose to be omitted from the study, or to withdraw from the study at any stage, there will be no detriment to your medical care or your career. If you choose to leave the study you should advise the study investigators. The study doctor has the right to withdraw you from the study if he/she feels it is appropriate to do so. This will be done if he/she feels that it is not in your best interest to continue either because of side effects of the drugs, or other injuries or illnesses you may experience during the deployment.

Should you not wish to participate in the study, you will require:

a) the normal prevention course for malaria of **doxycycline daily** during the deployment,
b) a malaria eradication course on returning to Australia including:
    i) two weeks of **doxycycline daily** and
    ii) two weeks of **primaquine three times a day**, and
c) all the required **blood samples** taken for deployment and post deployment screening.

SB 252263/033

Volunteer ID: _____

INFORMED WRITTEN CONSENT

I have carefully read the information provided to me in this information sheet and understand all the points addressed. All questions raised by me have been answered to my satisfaction. I have been given a copy of this Information Sheet and Consent Form. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.

I consent to my participation in the study

VOLUNTEER'S SIGNATURE _____

Printed Name: _____
Date: _____

INVESTIGATOR'S SIGNATURE _____

Printed Name: _____
Date: _____

DEFENCE PERSONNEL EXECUTIVE
DEFENCE HEALTH SERVICE BRANCH

CP2-7-66 Department of Defence CANBERRA ACT 2600

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PE 2000/15605/1
ADMEC 216/00
DHSB/ 3[illegible]/2000

Lieutenant Colonel P.E. Nasveld
Senior Medical Officer 7th Brigade
c/- Australian Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

Dear Lieutenant Colonel Nasveld,

AUSTRALIAN DEFENCE MEDICAL ETHICS COMMITTEE (ADMEC)
PROTOCOL 216/00: A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR

1. ADMEC has considered your protocol and approves in principle. However, some amendments to the information sheet and consent form are required before formal ethical clearance is given.

2. In particular, the Committee requires that the following action be taken:

   a. The consent form requires to contain the statement that "I understand that I can choose not to participate in or to withdraw from the study without detriment to my career or ongoing medical care", and

   b. The correct contact details for ADMEC must be included in the information sheet/consent form.

3. The correct contact details for ADMEC are:

   Executive Secretary
   Australian Defence Medical Ethics Committee
   CP2-7-66
   Department of Defence
   CANBERRA ACT 2600

4. Please note that this protocol will be considered to be "pending" until the required amendments are received and sighted by the Executive Secretary. If all requirements have been met, your project will be formally approved and a Researcher's Agreement forwarded for your signature.

5. Please contact me if I can be of any assistance.

Yours sincerely,

s22 [redacted]

V.R. ROSS
Lieutenant Colonel
Executive Secretary
Australian Defence Medical Ethics Committee

9 June, 2000

A randomized, double-blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor

Protocol Number SB 252263/033
ADMEC No. 216/00

INVESTIGATORS

Principal Investigators

Lt Colonel Peter Nasveld MBBS BScMed (Hons), Research Officer Clinical Studies AMI

Co-Investigators

Lt Colonel Mike Edstein PhD, Deputy Director AMI

Lt Colonel Peter Leggat MBBS BMedSc DTM&H DIH MMedEd MPH, Associate Professor, School of Public Health and Tropical Medicine, JCU

Major Scott Kitchener MBBS MPH, Research Officer Clinical Studies AMI

Medical Monitor (Australian Army, East Timor)

Capt Kym Ward MBBS, Regimental Medical Officer, 1 RAR

Study Co-ordinator (Australian Army):

Professor Karl Rieckmann MD, Director AMI

SPONSORS

SmithKline Beecham Pharmaceuticals, UK

s47F [redacted]

US Army Medical Research and Materiel Command (USAMRMC)

[redacted]

FINAL PROTOCOL: [redacted] May 2000
AMENDMENT 1: 22nd June 2000
AMENDMENT 2: 2nd August 2000

Summary of Protocol SB 252263/033

TITLE	A randomized, double-blind comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor
SPONSOR	SmithKline Beecham Pharmaceuticals, US Army Medical Materiel Development Activity (USAMMDA)
PLANNED STUDY START	October 2000
INDICATION	Replacement of existing prophylaxis protocol
PRINCIPAL INVESTIGATOR	LTCOL Peter Nasveld,
OBJECTIVES	The objectives of the study are to evaluate the effectiveness, safety and tolerability of tafenoquine and mefloquine for chemoprophylaxis against malaria infections.
STUDY DESIGN	Randomised, double-blind, comparative trial.
SAMPLE SIZE	Approx 600 - 700 volunteers
SELECTION CRITERIA	Volunteers recruited from exposed groups of soldiers serving in East Timor, who are non pregnant and not G6PD deficient
FORMULATIONS	Tafenoquine 200mg base Mefloquine 250mg base
ROUTE OF ADMINISTRATION	Oral
MAIN CLINICAL PARAMETERS: **EFFECTIVENESS** **SAFETY**	 Protection from malaria infections Adverse events Changes of laboratory values G6PD deficiency status Pregnancy testing Assessment of methaemoglobinaemia and phospholipidosis

PROCEDURES: **OUTCOME**	*Outcome measures* - positive malaria slide during the chemoprophylaxis phase and the 6 months following departure from East Timor
LABORATORY	Assessment of Parasitaemia Plasma Drug Levels Haematology Biochemistry G6PD Deficiency Screening Pregnancy testing Assessment of methaemoglobinaemia and phospholipidosis
DATA EVALUATION AND STATISTICAL ANALYSIS	*Safety analysis* – For frequently occurring AEs, the proportion of subjects reporting the AE will be compared between treatments using Fisher's exact test, and two-sided 95% confidence intervals will be used to estimate the difference in proportions between the treatment groups. *Effectiveness analysis* – A two-sided 95% stratified confidence interval will be calculated for the difference in proportion of prophylactic failures (tafenoquine – mefloquine). A conclusion of non-inferiority of tafenoquine will be drawn if the upper limit of this confidence interval is no more than 10%.

Study Flow Chart

Prophylactic Phase									*Relapse Follow-up Phase*				
Eligibility	✓							✓					
Physical exam	✓							✓	**Physical exam**		✓		
Medical history	✓												
ECG †	✓							✓					
Blood smear¶	✓				✓	✓	✓	✓					
Haematology / Biochemistry	✓			✓	✓	✓	✓	✓	**Biochemistry**		✓		
Plasma drug concentration #				✓	✓	✓	✓	✓					
Pregnancy test	✓				✓	✓	✓	✓	**Pregnancy test**		✓		
Baseline signs and symptoms	✓	✓											
Concomitant medication	✓	✓	✓	✓	✓	✓	✓	✓	**Concomitant medication**	✓	✓		
Adverse events			✓	✓	✓	✓	✓	✓	**Adverse events**	✓	✓		
Phospholipidosis † assessments	✓							✓	**Malaria status**	✓	✓	✓	✓
Methaemoglobin †	✓							✓					
Medication issued		✓	✓	✓	✓*	✓*	✓*	✓**					

* Medication actually issued weekly. ** Twice daily primaquine for eradication for two weeks following end of prophylactic phase. (Tafenoquine group receive placebo)

† Phospholipidosis, methaemoglobin and ECG measurements to be performed on a sample of 100 subjects only.

‡ The final visit of the prophylactic phase will be at 26 weeks for the majority of subjects. However, due to varied duties, some subjects may be deployed for a shorter or longer period. Therefore, the 'window' for the final prophylaxis visit is 26 +/- 4 weeks.

Samples for plasma drug concentration will be taken at varying times relative to dosing (day 1, 3, 5 and 7 after weekly dose of study medication). If a subject develops parasitaemia during the prophylactic phase, one additional sample will be collected at the time of developing parasitaemia and a second 12 weeks later. For any subject who develops parasitaemia during the relapse follow-up phase (up to week 12 only) a single sample will be collected at the time of diagnosis.

¶ Additional smears will be taken for any subject presenting with symptoms of malaria, and before doxycycline is commenced for any subject diagnosed with Rickettsia.

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[redacted]

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1. Summary

This study is a randomized, double-blind, comparative trial of the effectiveness, safety and tolerability of weekly tafenoquine and mefloquine for chemoprophylaxis of *Plasmodium falciparum* and *P. vivax* malaria in East Timor.

The objectives of the trial are to obtain safety and tolerability data over a six month period, to determine the weekly chemoprophylactic effectiveness of tafenoquine and mefloquine, and to assess the effectiveness of tafenoquine and primaquine in preventing post-deployment malaria. Additional objectives are to explore the population pharmacokinetics of tafenoquine and to monitor for phospholipidosis in the two treatment groups.

The study population will be an Australian Defence Force (ADF) infantry battalion on peace-monitoring duties in East Timor. The soldiers will be given (in a double-blind fashion) either a loading dose of daily 200mg tafenoquine over 3 days (total 600mg) followed by weekly 200mg tafenoquine for 6 months or a loading dose of 250mg mefloquine over 3 days (total 750mg) followed by weekly 250mg mefloquine for 6 months. Drug administration will be observed and subjects will be monitored for malaria parasitaemia by regular blood smears or immediately when malaria symptoms are suspected. Haematology, blood chemistry and adverse event questioning will be performed at each study visit (weeks 4, 8, 16 and 26). Assessments for phospholipidosis and methaemoglobinaemia will be performed on a sample of the study population prior to starting study medication and at the end of the 6 month prophylactic phase. At the end of the prophylactic phase, those soldiers on mefloquine will be given primaquine for the eradication of vivax malaria. In order to maintain the blind, soldiers who received tafenoquine during the prophylactic phase will be given dummy medication to match the primaquine. Both groups will be followed-up for 6 months after returning from East Timor (relapse follow-up phase).

During the relapse follow-up phase, subjects will attend visits at 6 and 12 weeks when they will be questioned on adverse events (including malaria relapse). In addition, at the 12 week visit, subjects will undergo a physical examination and blood chemistry. Subjects will be contacted further by phone at 18 and 24 weeks and questioned on malaria relapse in addition to review of the Central Malaria Register.

2. Introduction/Background

a. The Malaria Problem:

Malaria is a leading cause of morbidity and mortality in many developing countries with an estimated 100 to 300 million infections worldwide and 1.0-1.5 million deaths.[i] *P. falciparum* malaria is considered the most important malaria parasite because it causes high morbidity and mortality particularly in Africa, Southeast Asia, and the tropical zones of the Americas.[ii] Malaria has been, and continues to be a disease of military concern throughout the history of the Armed Forces through to the present.[iii]

The sporozoite form of the *P. falciparum* parasite is transmitted through the saliva of *Anopheles* mosquitoes as they feed on human blood during bites. Within minutes after inoculation, the sporozoites travel through the blood and invade the liver where they undergo asexual division

and mature.[iv] The pre-patent period (the time between the mosquito bite and the first appearance of plasmodia in the peripheral blood) for the *P. falciparum* parasite in man normally ranges between 9-12 days. The shortest reported pre-patent period in man is 5 days while the longest (in individuals not taking an antimalarial drug) is 25 days.[v] From the liver, merozoites are released into the blood and invade the erythrocytes, where they develop into schizonts. In the case of *P. falciparum* malaria, there are no residual parasites in the liver after the initial cycle of entry, division, maturation and release. Drugs active on the exoerythrocytic stage (i.e., the hepatic stage) of the parasite's life cycle are known as causal prophylactic drugs. They effectively disrupt the life-cycle of the parasites, preventing parasitaemia, systemic illness and further transmission. Drugs active on the erythrocytic schizonts are called blood schizontocides. These drugs are used to treat clinically apparent malaria infections, or as a suppressive prophylactic drug, which prevents clinical symptoms by destroying schizonts before they can cause illness.

There are currently no effective vaccines to prevent malaria infections. For non-immune individuals, drugs have been used over the years to prevent malaria. Although drugs such as chloroquine, pyrimethamine-sulfadoxine, mefloquine, and doxycycline have been used successfully in the past to prevent malaria infections, the advent of chloroquine-resistant strains of *P. falciparum* and *P. vivax* malaria parasites has necessitated the development of new drugs which can be used prophylactically to prevent malaria in those exposed to the parasite.

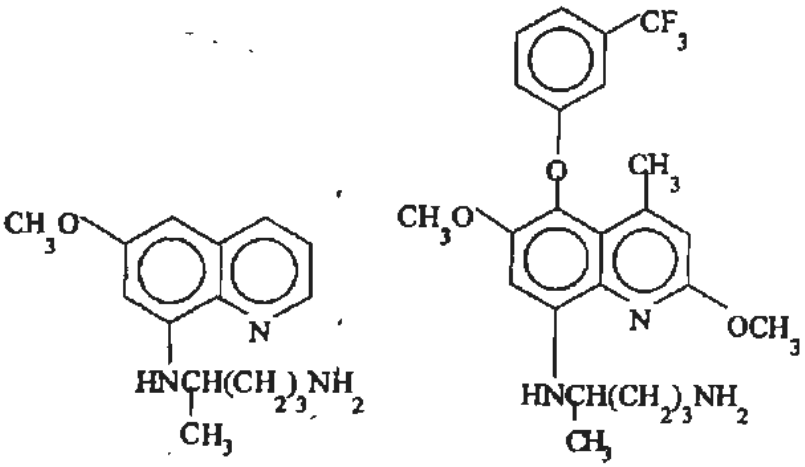
b. Current Drugs for Malaria Prophylaxis

At present, the principal drugs available for malaria prophylaxis are mefloquine and doxycycline. Mefloquine can be given weekly and is the usual recommendation given for travelers to Sub-Saharan Africa because of its high efficacy and weekly dosage regimen which is thought to enhance compliance.[vi] Mefloquine resistance is widespread in SE Asia and has been reported in Africa as well.[vii][viii] Mefloquine is used as suppressive prophylaxis against the erythrocytic stages of *P. falciparum* as well as *P. vivax* malaria. Doxycycline 100mg daily has been shown to be effective in western Kenya but it cannot be given to children and pregnant women and it often has distressing gastrointestinal adverse effects. Proguanil combinations such as atovaquone/proguanil (Malarone®, Glaxo Wellcome) have been shown effective against intense falciparum malaria exposure in western Kenya and so has azithromycin (Zithromax®, Pfizer).[ix,x] Both require daily medication and thus have less than ideal compliance characteristics.

c. Test Article: tafenoquine (WR 238605)

Tafenoquine is an 8-aminoquinoline with an additional methoxy group at the 2 position, a methyl group at the 4 position, and a 3-trifluoromethylphenoxy substitution at the 5 position of the quinoline ring. It is "an excellent candidate for clinical evaluation as: (1) a causal prophylactic; and/or (2) a blood schizonticidal drug against human malaria parasites, including poly-resistant *P. falciparum* and chloroquine-resistant *P. vivax*".[xi] It is administered as a succinate salt and not as a free base.

The structure of tafenoquine (as the free base) and the related 8-aminoquinoline primaquine are shown:



Primaquine **Tafenoquine**

i. Pre-Clinical Pharmacology, Toxicology and Pharmacokinetics

The pre-clinical efficacy, toxicology and pharmacokinetics are summarised in the Investigator Brochure.

ii. Previous Human Experience

Clinical Pharmacology Studies:

To date, tafenoquine has been administered to a total of 238 healthy volunteers in Phase I clinical pharmacology studies. The first study in man was a rising, single oral-dose safety and tolerance study in 48 male volunteers receiving doses from 4 to 600 mg base fasting.[xii] The subjects tolerated all doses well. Sporadic complaints of mild headache and gastrointestinal symptoms were noted. There were sporadic, borderline elevations of transaminases, although they occurred in placebo controls with the same frequency and degree. Preliminary kinetic analysis of plasma samples from this study indicated that peak plasma levels occur at about 12 hours and increase linearly with dose. The half-life was at least 14 days, and appeared to be independent of dose. Whole blood concentrations were 1.75 fold greater than plasma concentrations, indicating that tafenoquine accumulates inside the red cell

The second study investigated the pharmacokinetics, pharmacodynamics, safety and tolerance of a single oral dose of tafenoquine succinate in 18 male volunteers.[xiii] Three groups of six fasting volunteers received 100, 200 and 400 mg. Tafenoquine was well tolerated. Sporadic mild complaints of headache and abdominal distress (gas, loose stools) were reported. One individual had mild elevation of serum transaminase enzymes after drug administration. However, upon review of his past records, it was noted that he

had chronic borderline liver function test abnormalities. His values returned to his baseline during the follow-up period. A one-compartment model with a mean elimination half-life of 14.8 +/- 2.0 days best described the plasma and blood tafenoquine levels from this study.

The third study was a placebo-controlled, randomized pilot study to evaluate whether a single 600 mg oral dose of tafenoquine, when administered 1 day before sporozoite inoculation, could prevent parasitemia in non-immune male and female volunteers.[xiv] In this study, four volunteers received drug and two received placebo while fasting. The subjects who received placebo developed parasitemia and clinical malaria ten days after inoculation. Of the four on drug, three were completely protected by the single dose, whereas the fourth subject developed malaria on day 30. The peak blood concentration of tafenoquine in this individual was 244 ng/ml; in contrast, the three who were completely protected had peak levels of 417-489 ng/ml. Two drug-treated individuals had loose stools within hours after receiving drug, and one of these two was the individual who developed malaria. This gastrointestinal side effect may have resulted in the reduced drug concentrations.

The fourth study was a randomized, double-blind, placebo-controlled, multiple-dose safety and tolerance.[xv] Thirty-six male and female subjects were enrolled, divided into three groups of 12. The three groups received weekly oral doses of 200, 400 and 600 mg/week for 10 weeks, respectively, while fasting. In each group of 12, eight subjects were randomly assigned to receive drug and four to receive placebo. A study report has not yet been received. However, correspondence with the study investigator has revealed that side-effects possibly due to study drug have all been mild and include: gastrointestinal disturbances (nausea, vomiting, diarrhea), headache, light-headedness and dysgeusia. Methaemoglobin levels of up to 5% have been seen, and there were no abnormal trends in the remaining clinical labs or pulmonary function tests. While all three regimens were safe, the high dose was not thought to be well tolerated on an empty stomach due to the frequency of the gastrointestinal effects.

The fifth study was a randomized, double-blind, placebo-controlled multiple-dose prophylaxis study against *P. falciparum*.[xvi] Five non-immune volunteers were randomized to receive a loading dose of 600 mg on days -3 and -2 before sporozoite inoculation of the NF54 strain of *P. falciparum* using a standard mosquito inoculation model (day 0), followed by an additional 300 mg dose on days 5, 12, 19 and 26 (suppressive arm). Five additional volunteers were randomized to receive the same loading dose regimen (days -3, -2 and 5) with placebos on days 12, 19 and 26 (causal arm). Two volunteers received placebos at all dosing times. All doses were administered with breakfast. When it became apparent that the proposed regimen was not completely causally prophylactic in this setting, those volunteers in the causal arm were changed to the suppressive regimen, and also received the 300 mg maintenance doses for the last three weeks. All but one of the volunteers had positive parasite cultures. Six out of the ten drug treated individuals developed asymptomatic parasitemia. Five of these six were treated with chloroquine. The sixth was not treated and the parasitemia cleared. *In vitro* blood schizonticidal sensitivity studies suggested that the NF54 parasite is several times less susceptible to tafenoquine than most others isolates - even new multi-drug isolates

from South-East Asia. This would suggest that if tafenoquine has causal prophylaxis activity, the dosing regimen used may not protect against all strains. The fact that these non-immune individuals, infected with parasites that are relatively resistant to study drug, had low parasite counts (<25 / ul) and no symptoms suggests that the weekly 300 mg dose may be close to being a completely suppressive regimen, and doses close to this should be studied further. The volunteers complained of mild, transient episodes of abdominal cramping, diarrhea and headache, lasting for a few hours after drug administration. Methemoglobin levels of up to 8% were seen. Preliminary concentration data suggest that co-administering tafenoquine with food may increase bioavailability 50% compared to the fasting state.

Phase II Studies:

In 1997, 235 subjects in Lake Victoria region of Kenya were treated in a study investigating a number of tafenoquine regimens for prophylaxis against malaria infection in this highly endemic region for *P. falciparum*. In this study, as in all other Phase I and II studies, subjects deficient in Glucose 6 Phosphate Dehydrogenase (G6PD) were excluded due to the known 8-aminoquinoline class-effect of inducing hemolysis in G6PD deficient individuals. In this placebo-controlled, double-blind, randomised study, the tafenoquine regimens were 200 mg for three days followed by 200 mg weekly for up to 13 weeks, 400 mg for three days followed by 400 mg weekly or 400 mg for three days followed by placebo weekly. Tafenoquine (either 200 or 400 mg base) given weekly was highly efficacious (around 90% protective efficacy) in preventing malaria infection in adult semi-immune subjects on a background of a 92% malaria attack rate in the placebo group. The three day only regimen gave 91% protective efficacy after seven weeks of exposure to malaria infection. The one serious drug-related adverse event was hemolysis in a woman whose G6PD test was incorrectly recorded. Despite the long half-life of tafenoquine (>2 weeks), following a two unit blood transfusion to restore her erythrocyte volume the volunteer did not experience any further drug-induced hemolysis on follow up of several months. One other asymptomatic hemolytic event was detected, also in a woman who was entered in error to the study despite being G6PD deficient. Otherwise tafenoquine was found to be safe and well-tolerated. Gastrointestinal disturbances were found to be higher in the tafenoquine groups than placebo and appeared to be higher on the 400mg than the 200mg weekly regime. Another known class-effect of 8-aminoquinolines, that of elevated methemoglobin levels, was seen to a limited degree on treatment with tafenoquine, with levels rising to mean peaks of 2.5% on 200 mg weekly and 4.5% on 400 mg weekly; there were no obvious side-effects evident that could be associated with these elevations.

In 1998, 205 members of the Royal Thai Army stationed on the Cambodian border participated in a double-blind, randomized, placebo-controlled trial of tafenoquine prophylaxis. Approximately half of the subjects received a 400 mg loading dose for 3 days followed by 400 mg monthly for 5 months; the remainder receiving placebo. Twenty-seven cases of malaria (18 *P. vivax*, 8 *P. falciparum*, and 1 mixed) occurred in the placebo group versus just one case of *P. vivax* malaria in the tafenoquine group. The overall protective efficacy was >95%. Nausea, loose-stools and dizziness occurred at a

higher incidence on tafenoquine (around the 4-6% level) compared to placebo (around the 1-2% level).

In 1998/99, 513 semi-immune adult subjects were randomized and treated in a 12-week dose-ranging, randomized, double-blind, placebo-controlled trial in northern Ghana. Following radical cure with quinine, doxycycline, and primaquine, subjects were randomized to tafenoquine 25 mg, 50 mg, 100 mg and 200 mg or placebo, administered daily for three days followed by once-weekly. Sixty five percent of the subjects in the placebo group were infected with *P. falciparum* over the course of the study, whilst protective efficacy was around 85% in the three highest dose tafenoquine groups. Some evidence of transiently increased serum transaminase enzymes were noted, but these were considered to be specific to this study and not clinically significant. The drug was well-tolerated, with no notable on-treatment trends.

A double-blind, randomized, placebo-controlled dose-ranging study was carried out in Gabon in 1999 assessing the prophylactic efficacy of a three day course of tafenoquine. A total of 415 immune subjects between 12 and 20 years of age were treated with halofantrine (250 mg/day for 3 days) to clear any pre-existing parasitemia followed by a loading dose of 25 mg, 50 mg, 100 mg, or 200 mg base of tafenoquine daily for 3 days, or placebo; they were then followed for 70 days. A placebo attack rate of 29% was seen over the duration of the study. At 70 days, the three day 200 mg tafenoquine dosing regimen gave a protective efficacy of 100%, with a dose-dependent decrease in efficacy below this dose level. Abdominal pain was the only adverse event which was reported at a higher incidence by subjects following treatment with tafenoquine (up to 12%) compared to the placebo group (5%).

In 1998/99, 376 members of an Australian Army peace-keeping force deployed to the island of Bougainville received tafenoquine, 400 mg daily (as a single dose or a split dose of 200 mg x 2) for 3 days, while another 210 soldiers received primaquine 22.5 mg daily for 14 days at the end of their tour. Of the 4 regimens containing tafenoquine in this study, 2 also included doxycycline and/or chloroquine. Both primaquine regimens also included doxycycline and/or chloroquine. This was a randomized open-label design with the aim of evaluating tafenoquine in the role of a post-exposure prophylactic agent to eradicate and prevent *vivax* malaria. There were 7 *P. vivax* eradication failures (ie. relapses) in each of the tafenoquine and primaquine groups, occurring between 6 and 20 weeks after leaving Bougainville. Gastrointestinal disturbances (abdominal pain, nausea, dairrhea and, in a limited number of individuals, vomiting) were reported at a higher incidence on tafenoquine in this open-label study compared to primaquine. Splitting the tafenoquine dose to 200 mg twice daily appeared to reduce the incidence of gastrointestinal disturbance. Following these experiences, further evaluation of tafenoquine as a post-exposure prophylactic have been gained in troops returning from deployments in East Timor. Firstly a cohort of 392 troops were treated (in a 2:1 ratio of tafenoquine:primaquine) with a three day course of tafenoquine 200 mg twice a day. This was followed by a further 569 troops, 402 of which received a three day course of 200 mg tafenoquine once a day and 167 of which received a standard primaquine eradication course. These troops are currently still being followed for efficacy and safety endpoints.

Two additional studies in Thailand evaluated the safety and efficacy of tafenoquine in the prevention of relapse of *vivax* malaria following an acute infection[xvii]. The first study compared a number of dosing regimens of tafenoquine (300mg daily for seven days; 500mg daily for three days followed by a repeat regime one week later; a single dose of 500 mg), following chloroquine blood schizontocidal treatment, to chloroquine alone. Forty four patients in total were involved in the study and were followed for up to 6 months after treatment to evaluate the rate of *vivax* relapse. In the second study further tafenoquine dosing regimens (300mg daily for seven days; 600mg daily for three days; a single dose of 600 mg), following chloroquine blood schizontocidal treatment, were compared to chloroquine alone or chloroquine followed by a standard eradication course of primaquine. Eighty patients were included in this second study. Across the studies, in patients completing >2 months of follow-up, the incidence of cure (ie. lack of relapse) was between 86% and 100% on the tafenoquine regimes, compared to 20-43% on chloroquine alone and 75% on primaquine. In these studies there was evidence of some gastrointestinal disturbance associated with the administration of tafenoquine.

Overall this data suggests that tafenoquine is safe, well-tolerated and effective whether used in chemoprophylaxis of malaria, in eradication following an acute *P.vivax* infection or as a post-exposure prophylactic against *P.vivax* relapse. Based on safety and tolerability data, efficacy data from dose-ranging chemoprophylaxis studies and pharmacokinetic data gathered during Phase I and II, a dose of 200 mg daily for three days followed by 200 mg weekly has been selected as the dose to take into Phase III studies to evaluate tafenoquine as a chemoprophylactic agent. This is regarded as the highest, well-tolerated dose and is several increments above the shoulder observed in the chemoprophylactic efficacy dose-response curve.

Please refer to the Investigator Brochure for a more complete review of the clinical data on tafenoquine.

d. Test Article: mefloquine

Mefloquine in recent years has replaced chloroquine as a single agent prophylactic against chloroquine-resistant *P. falciparum*. Mefloquine, which has a long half-life, was used originally as an every other week dose. Since there were prophylactic failures of *P. falciparum* with this dosing regimen, once weekly dosing is now recommended. [xviii]

Although mefloquine is generally well-tolerated at prophylactic doses, it also is not without side effects. Neuropsychiatric side effects (such as dysphoria, dizziness, and rarely seizures, psychosis) have been reported, but the incidence is not significantly different with respect to chloroquine when tested in a blinded manner.[xix] Western travelers tend to have many complaints that often focus on their antimalarial prophylaxis. A recent survey of British tourists found that 40% complained of some problem that they related to malaria prophylaxis.[xx] The complaints were not different between mefloquine or proguanil combined with chloroquine except for neuropsychiatric adverse events which were significantly more common in mefloquine users. Still, less than 1% of travelers taking mefloquine complained of disabling neuropsychiatric adverse events.

Although mefloquine resistance has been documented in *P. falciparum* on the Thai-Cambodian and Thai-Burmese borders, mefloquine continues to be effective elsewhere, including Vietnam[xxi] The IC_{50} of mefloquine against a chloroquine-resistant, mefloquine-sensitive clone of *P. falciparum* (W2) is about 0.6 ng/ml; against a chloroquine-sensitive, mefloquine-resistant clone (D6), the IC_{50} is approximately 4 ng/ml. The metabolism of mefloquine is incompletely understood. However, it appears that one of its metabolites is 2,8-bis (triflouromethyl) -4-quinoline carboxylic acid is active; its antimalarial role, if any, has not been well-established.

Mefloquine HCl is used for both treatment and prophylaxis. The treatment regimen as labeled (Lariam®) consists of a single dose of 10-25 mg/kg (base) as a single or split dosage. For prophylaxis, mefloquine is given as a single dose of 250 mg weekly.

The pharmacokinetics of mefloquine has been reviewed.[xxii] Mefloquine is rapidly absorbed, with a bioavailability of around 85%. The volume of distribution is less than that of chloroquine and ranges between 9 and 50 l/kg. Following a single 250 mg dose of mefloquine HCl given to healthy males, the mean time to peak was 13.5 hours.[xxiii] The mean half-life was 292 hours (range 155-503); it is modeled best using a one- or two-compartment model.[xxiv]

The serum concentrations necessary for mefloquine to be effective have not been well-established. In a study in which Peace Corps volunteers' mefloquine serum concentrations were determined after their most recent mefloquine dose and correlated with *P. falciparum* breakthroughs, the failures occurred in the second week after their last dose. However, although serum mefloquine concentrations decreased gradually over the two week time period, the correlation of serum concentrations between failures and non-failures was poor.[xxv] Serum concentrations of mefloquine in those volunteers who failed prophylaxis ranged from 62-398 ng/ml (mean 262 ng/ml). However, there were other individuals who had similar concentrations in the first week.

In another study, an attempt was made to correlate mefloquine treatment failures with serum mefloquine concentrations and resistance patterns of *P. falciparum in vitro*.[xxvi] The authors were unable to find a positive correlation. In yet another study, blood concentrations were not associated with treatment outcome.[xxvii] The reasons for the lack of pharmacodynamic-pharmacokinetic correlation are unknown.

3. Rationale and Justification for Investigation

The current accepted regimen for the management of malaria for the ADF is the combination of daily chemosuppression (doxycycline 100mg base) during exposure, followed by an eradication course for two weeks (doxycycline 100mg daily and primaquine 7.5mg base three times a day). This addresses the blood stages during exposure and eradication, and the liver stages of the parasite life cycle in eradication. The regimen suffers compliance problems arising from frequency of medication and side effects. It fails to manage the early hepatic stages of the parasite (*P. vivax*) addressing this aspect of the life cycle only during eradication when hypnozoites (an hepatic phase of the malaria life cycle) are more mature. Recent experience in Bougainville and other areas of PNG suggests that the ineffectiveness of the primaquine course remains a major health problem after the return of ADF personnel from malarious areas of the Southwest Pacific region.

Tafenoquine is a new 8-aminoquinoline drug developed by Walter Reed Army Institute of Research (WRAIR). It is more active and generally less toxic than primaquine. Preliminary data from studies in Kenya suggest that tafenoquine may be more toxic in inducing haemolysis in G6PD deficient individuals than primaquine. The compound has been well tolerated at doses of 1200mg base over three consecutive days during trials recently in Bougainville. Studies with the Royal Thai Army (RTA), along with the ADF Bougainville trial, have produced data on the plasma levels of tafenoquine following monthly prophylaxis and radical cure, respectively. In each trial the volunteers received a loading dose of 1200mg tafenoquine over 3 days (400mg base for 3 consecutive days). The Thai soldiers achieved peak tafenoquine values of about 730 ng/ml at 12 hours post last dose compared with 560 ng/ml in Australian soldiers. The difference between peak levels may be due to a combination of ethnic differences and body weight, with Australian soldiers weighing 25% more than Thai soldiers.

In the RTA trial the mean trough plasma level of tafenoquine after monthly dosing (400mg) was about 80-100 ng/ml. Of the 104 soldiers who were on tafenoquine only one soldier came down with vivax malaria. This soldier, who appears to rapidly clear tafenoquine, had a plasma level of 40 ng/ml when diagnosed with malaria. The elimination half-life of tafenoquine in Thais was estimated at 16 days, which is comparable to 14 days in Caucasian studies.

Recently, tafenoquine (400mg daily over 3 days) has been evaluated for eradication of vivax malaria in ADF personnel returning to Australia following 2-4 months deployment on peace-monitoring duties in Bougainville, PNG. The trial commenced in January 1999 and, so far after one year, fourteen Australian soldiers have come down with vivax malaria after returning to Australia. Of these seven received primaquine and seven received tafenoquine. All presented with malaria more than six weeks after returning to Australia.

As discussed above, the present regimens for malaria prophylaxis fail to address the early liver stages of the parasite. From the experiences discussed, it is believed that the mature *P. vivax* hypnozoites become refractory to either primaquine or tafenoquine[xxxviii]. Consequently, the administration of tafenoquine as a chemosuppression agent in the course of exposure to malaria, addresses the early hepatic stages of the parasite and this stage is likely to be more sensitive than the mature forms. With both tissue and blood stage activities, tafenoquine should be an effective prophylactic agent.

Drug concentration and effectiveness are affected by genetic factors, specific immune status and varying susceptibility of malaria parasites. Primaquine (30 mg daily) has been reported to be highly effective (>90%) in preventing falciparum and vivax malaria[xxxix]. At this dose, peak primaquine concentrations of 100 ng/ml could be expected[xxxx]. The determination of an arbitrary minimum acceptable plasma level of tafenoquine is based on previous primaquine data, the greater antimalarial activity of tafenoquine and experience of blood stage malaria parasites breaking through around 40-50 ng/ml. Thus, a plasma tafenoquine concentration of 100 ng/ml is considered an arbitrary minimum value providing a 2-fold margin of protection. Based on the tafenoquine plasma data from the RTA and ADF trials and a half-life value of about 14 days for tafenoquine, 200mg tafenoquine weekly is expected to produce minimum weekly plasma tafenoquine levels of 150-250 ng/ml, which should be adequate to protect ADF personnel from malaria infections.

In this study we propose to compare the chemosuppressive effectiveness of weekly tafenoquine and mefloquine and to obtain side effect data on both drugs over a six month period (plus three months of the relapse follow-up phase). Mefloquine is one of the most widely used drugs for the chemoprophylaxis of malaria and is recommended by the World Health Organization and the Centers for Disease Control (USA) for protection against chloroquine-resistant falciparum malaria.

Tafenoquine may be found to be more effective than mefloquine in preventing malaria infections as:

- the hepatic stages of *P. vivax* are sensitive to tafenoquine, though not to mefloquine alone;
- the blood stages of *P. vivax* and *P. falciparum* are sensitive to tafenoquine, as for mefloquine;
- the sexual stages (gametocytes) of both species are sensitive to tafenoquine, whereas mefloquine has no gametocytocidal activity;
- Compliance with a weekly dose of tafenoquine should be comparable with weekly mefloquine
- tafenoquine weekly may have fewer or different adverse effects than weekly mefloquine

Finally, there is an acute military and civilian need for new antimalarial drugs for the chemoprophylaxis of malaria.

4. Objectives

a. Primary Objective

- To compare the safety and tolerability of tafenoquine and mefloquine over a 6 month treatment period

b. Secondary Objectives

- To assess the effectiveness of tafenoquine and mefloquine for chemoprophylaxis of *P. falciparum* and *P. vivax*
- To assess the effectiveness of tafenoquine and primaquine in preventing post-exposure malaria
- To characterise the population pharmacokinetics of tafenoquine and evaluate the effects of various subject characteristics on tafenoquine pharmacokinetics
- To monitor for phospholipidosis, or effects of phospholipidosis, in man

5. Study Design Overview

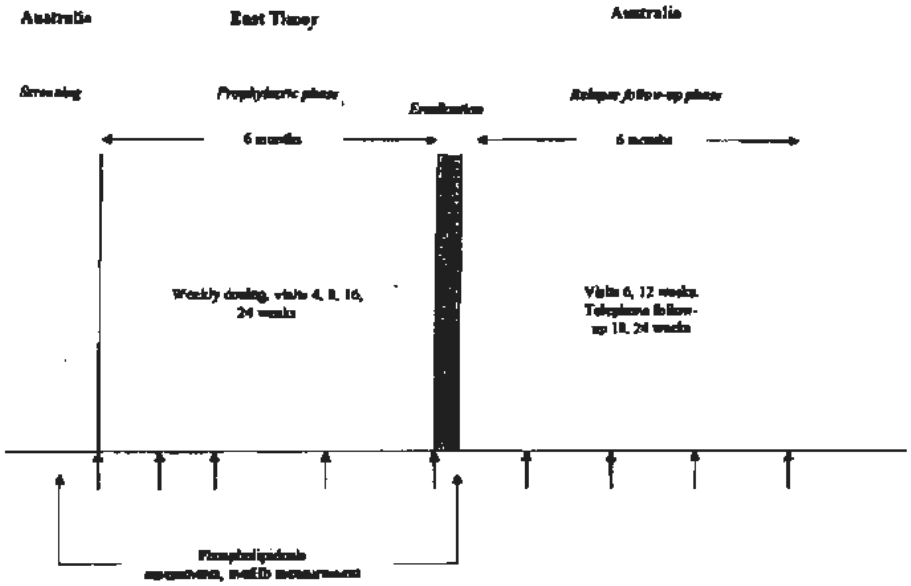
a. Study Design

The study is a double-blind, randomized clinical trial comparing the effectiveness, safety and tolerability of tafenoquine and mefloquine for chemprophylaxis of malaria infections in non-

immune Australian Defence Force (ADF) personnel deployed to a malarious area. The prophylaxis regimens will include a loading dose during pre-deployment training in Australia of 600mg tafenoquine (200mg daily for three days) or 750mg mefloquine (250mg daily for three days). All volunteers will subsequently receive either 200mg tafenoquine or 250mg mefloquine weekly. The chemoprophylactic trial period ('prophylactic phase') is six months with a follow-up period of a further six months ('relapse follow-up phase').

Subjects will be randomised to treatment in a ratio of 3:1 (tafenoquine : mefloquine).

b. Schedule of Assessments



6. Study Population / Location

The target population is an ADF infantry battalion on peace-monitoring operations on the island of East Timor. Volunteers will be in a malarious area for a continuous period of approximately six months during the deployment. All personnel will receive pre-deployment medical screening including assessment of G6PD deficiency status. Those personnel found to be G6PD deficient will not be involved in the trial and will (in the normal course of events) commence the standard ADF prophylaxis course of doxycycline 100mg daily beginning two days prior to deployment, to be continued for two weeks (along with primaquine) following re-deployment.

a. Number of Subjects

Approximately 650 subjects will be randomised in a 3:1 ratio (tafenoquine : mefloquine). An assumed drop-out rate of 5% will allow for at least 600 evaluable subjects (450 on tafenoquine, 150 on mefloquine).

Phospholipidosis,methaemoglobin and ECG assessments will be performed on a sample of approximately 100 subjects (one Company of the Battalion). The Company to be selected will be decided according to operational logistics immediately prior to deployment.

b. Inclusion Criteria

1. Healthy male or female volunteers between the ages of 18 and 55 years inclusive
2. Medical Class 1 or 2* (Australian Army standard)
3. Those giving informed consent and able to comply with the procedures of the protocol

* Medical Class 1: Fit for deployment and employment in trade in any operational environment.
Medical Class 2: Fit for employment and generally fit for deployment subject to a pre-deployment check based on geographic restriction or access to health support.

c. Exclusion Criteria

1. For females, those pregnant, lactating or unwilling/unable to comply with recognised contraceptive methods during the prophylaxis stage of the study and for a period of 12 weeks after cessation of administration of study drugs .
2. Demonstrated glucose-6-phosphate dehydrogenase deficiency (two separate tests to be performed at screening unless the result of a previous test is present in the subject's medical notes, in which case just one test is required. The result must be 'normal' for both tests).
3. History of allergy or intolerance to mefloquine, primaquine or any other 8-aminoquinolines.
4. Clinically significant abnormalities (to include, but not limited to, abnormal hepatic or renal function) as determined by history, physical examination, or laboratory testing of blood chemistry and haematology.
5. History of psychiatric disorders and/or seizures.
6. Laboratory guideline values for exclusion are values Hb <12 g/dl for males or < 10 g/dl for females, platelets < 100,000/mm^3, WBC < 3000/μl^3, creatinine > 0.16 mmol/l, ALT > 150 U/l, AST > 120 U/l, bilirubin > 40 µmol/l and GGT > 150 U/l.
7. Subject has received another investigational drug within 30 days or 5 half lives (whichever is longer), of study start.
8. Subject has taken any antimalarial drug within the past 2 weeks.
9. History of drug or alcohol abuse.

7. Conduct of the Study

a. Ethics and Regulatory Considerations

The study will be conducted according to current Good Clinical Practice guidelines (ICH GCP) and the Declaration of Helsinki (see Appendix A).

The protocol will be submitted for appraisal and approval by the Australian Defence Medical Ethics Committee (ADMEC). Regulatory approval (Clinical Trial Notification) will be obtained from the Therapeutic Goods Administration (TGA) in Australia. Approval will also be obtained from the US Army Human Subject Research Review Board (HSRRB).

If amendments to the protocol are required, they will be submitted in writing to all relevant bodies as described above. Written approval of any such amendments must be received by SB/USAMRMC prior to the application of the amendment in the study. A revised Information Sheet and Consent Form will reflect any such changes to the protocol if necessary.

i. Ethics Review Committee (ERC)/Institutional Review Board (IRB)

ERCs/IRBs must be constituted according to the local laws/customs of each participating country.

This protocol will be submitted to an appropriate Committee or Board (as detailed in a above) and their written unconditional approval obtained and submitted to the sponsor before commencement of the study. SB will supply relevant data for the investigator to submit to the hospital/university/independent ERC/IRB for the protocol's review and approval. Verification of the ERC/IRB's unconditional approval of the protocol and the written informed consent statement will be transmitted to SmithKline Beecham prior to shipment of drug supplies and CRFs to the site. This approval must refer to the study by exact protocol title and number, identify the documents reviewed and state the date of review.

The ERC/IRB must be informed by the investigator of all subsequent protocol amendments and of serious or unexpected adverse experiences occurring during the study which are likely to affect the safety of the subjects or the conduct of the study. Approval for such changes must be transmitted in writing to SmithKline Beecham and MRMC via the investigator.

ii. Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki (Protocol Appendix A) will be implemented in this study before any protocol-specified procedures or interventions are carried out.

Information will be given in both oral and written form whenever possible and deemed appropriate by the ERC/IRB. Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to enquire about details of the study.

The consent form generated by the investigator with the assistance of SB, must be approved (along with the protocol) by the ERC/IRB and be acceptable to SB. Consent forms must be in a language fully comprehensible to the prospective subject. Informed consent shall be documented by the use of a written consent form approved by the ERC/IRB and signed by the subject.

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations. This form may be read to the subject but, in any event, the investigator shall give the subject adequate opportunity to read it before it is signed.

Consent must be documented by the dated signature of the subject. The signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or SB/MRMC professional and Regulatory Compliance persons.

Informed consent will be obtained in the following way: 1 month prior to deployment, educational sessions focussing on vector borne disease will be conducted for all troops and units deploying to East Timor with the 1 RAR Battalion Group. The study will be introduced at this stage with briefing in Company sized groups (approximately 100). Potential subjects will be given a copy of the information sheet at this stage. If still interested, they will be asked to register an "expression of interest" and their details will be entered on a screening log. Approximately 2 weeks prior to deployment, those who indicated interest will be further briefed by the Investigators and "Informed Consent" obtained in groups no greater than Platoon size (29 soldiers). The Platoon Commander and Sergeant will be interviewed separately to the remainder of the Platoon to reduce the likelihood of "undue influence". Once formal informed consent has been obtained, subjects will enter the screening phase of the study. The "Ombudsman" role for this study will lie with the Senior Health Officer North Queensland who is not involved in the study but holds responsibility for the delivery and quality of health care in Townsville, from where the volunteers will be selected. The current occupant of this position is LtCol Carmel Van Der Rijt, Clinician and Commanding Officer of Lavarack Barracks Medical Centre (LBMC) which will be providing laboratory and X-ray support to the study.

iii. Randomization and Volunteer Identification

Randomization will be by a predetermined blocked randomisation procedure, and will be stratified by Company. Volunteers will be randomized individually into one of the two groups using blocked randomisation. The master code linking medication number to treatment group will be kept by SB. Individual code break envelopes will be provided to the investigator, and copies will also be held by SB.

iv. Risks

All volunteers will be at risk of malaria infection. Estimates from the western border of East Timor, where the soldiers will be deployed, indicate that the entire battalion will be at high risk of developing malaria. All volunteers are accepting, as part of the study, the possibility of clinical events either known or unknown associated with the study medication. The primary clinical events associated with tafenoquine include gastrointestinal disturbances (vomiting, nausea, diarrhoea) and headaches. Recent studies by AMI in Bougainville (Papua New Guinea) using tafenoquine for the eradication of vivax malaria indicate that the side effects are not significantly different to those of

primaquine. Further, it has been found that taking the medication with food reduces the occurence of these events. The most significant adverse event is the possibility of haemolysis when tafenoquine is given to those individuals with a G6PD deficiency. Subjects will be excluded if found to be G6PD deficient, and thus the risk of such an event will be substantially reduced.

As regards volunteers on mefloquine, the most frequent adverse effects are nausea, diarrhoea, vomiting, abdominal pain and dizziness. Although rare, neurological disturbances such as depression and seizures have also been reported with mefloquine. The adverse effects associated with mefloquine appear to be no more toxic than other prophylactic schedules.

Phlebitis is a possible consequence of venepuncture, however, this will be necessary for post-deployment screening regardless of volunteering for the study. Additional risk occurs from pre-entry blood testing and research monitoring for haematological and biochemical parameters, and the exclusion of parasitaemia.

v. **Benefits**

Malaria is a very serious and debilitating disease resulting in disruption of usual activities. Thus, protection from such an infection is a real benefit. The principal benefit in this study is the possibility of improved protection from malaria infections (ie. reduced morbidity and mortality). It is expected that greater convenience from a weekly prophylaxis agent will generate fewer reported side effects and improved compliance.

b. General Instructions

To enhance bioavailability, and minimise side effects of tafenoquine and mefloquine, all medication is to be taken with food. Both regimens are expected to produce trough steady-state plasma values ranging from 150-250 ng/ml for tafenoquine and 400-800 ng/ml for mefloquine in Australian soldiers. No separate malaria eradication will be given for the tafenoquine group after leaving the malarious area. However, for those in the mefloquine group, primaquine 15mg base twice a day will be taken for 14 days following departure from the malarious area.

Volunteers will be monitored at 4, 8, 16 and 26 (+/- 4) weeks during the prophylactic phase of the trial. They will subsequently be monitored at 6 and 12 weeks following their return to Australia, and further telephone follow-ups will take place at weeks 18 and 24 of the relapse follow-up phase. Monitoring and dosing are summarised in the study flow chart at the front of the protocol (see page 4).

Blood smears will be identified by their unique subject number for screening by a blinded microscopist, recording the number of parasites per 500 white cells counted.
Prophylaxis failure will be defined by the development of a single positive blood smear for malaria parasites (either with or without symptoms). Any volunteer who does develop malaria during the study will be treated according to current clinical practice (e.g quinine plus doxycycline for *P.falciparum* infections or chloroquine for *P.vivax* infections) but withdrawn from the study.

Volunteers will be issued with an identification card indicating their involvement in the study. The card will contain guidelines to treating Medical Officers on the commencement of treatment, and will contain a pager number for contacting the duty Clinician of AMI.

The study ID card will also advise the treating Medical Officer of the requirements to provide AMI with confirmatory blood slides taken when a volunteer presents with fever, and for three consecutive days following onset of fever. Should treatment be initiated following confirmation of malaria by a regional laboratory, instructions for the collection of a plain and an EDTA sample of venous blood for forwarding to AMI (and thence to SB where necessary) for *Plasmodium* speciation (via Polymerase Chain Reaction techniques) and drug level analysis will also be included. Additionally, serial blood slides to determine clearing of parasitaemia will be detailed. The duty clinician at AMI will arrange transport of all samples to AMI by courier.

Diagnosis and treatment of Rickettsia during prophylactic phase:

Treatment of Rickettsia includes the use of doxycycline, a drug which is also effective in the chemoprophylaxis of malaria. However, if a subject is diagnosed with Rickettsia during the prophylactic phase of the study, withdrawal from the study is not necessary (unless otherwise indicated), but an additional blood smear will be performed to assess parasitaemia. This blood smear must be performed before doxycycline treatment is commenced. The subject will remain in the study but data from the point of treatment with doxycycline onwards will be excluded from the efficacy analysis.

c. Study Procedures

i. Collection and preparation of blood samples

Whole venous blood will be collected by venepuncture by qualified personnel at screening†, on the final day of the loading dose of study medication (Day 2) and at weeks 4, 8, 16 and 26 of the prophylactic phase. A further blood sample will be taken 12 weeks into the relapse follow-up phase.

Samples for all study analyses will be collected at each visit into one 4 ml EDTA tube and one 5 ml serum separation (SST) tube. The samples at the end of the 6 month prophylactic phase, and after 12 weeks of the relapse follow-up phase, will be taken in conjunction with other samples required as a component of post-deployment screening.

Thus, for study purposes, a maximum of 7 blood samples (each of 9ml) will be collected from the majority of subjects during the trial period (total 63ml). However, additional blood will be collected from a selected sample of subjects for assessment of phopholipidosis and methaemoglobinaemia (see sections (v) and (vi) below). For each of these subjects, an additional 20ml of blood will be required. Additional blood samples (maximum 5ml per sample) will be taken from any subject who develops malaria during the prophylactic phase of the study.

All blood samples will be refrigerated in a portable fridge at 4°C. From the 4 ml EDTA tube, two blood smears will be prepared followed by haematological analysis. The remaining blood in the EDTA tube and 5 ml SST tube will be centrifuged for 10 minutes at 2500-3000 rpm to produce plasma (EDTA tube) and serum (SST tube) samples. Biochemical analysis will be carried out on the separated serum. Remaining plasma and serum will be stored (at –20°C whilst in East Timor and at -70°C in Australia) until analysed. Drug concentration analysis will be performed on the remaining plasma.

†The sample taken at screening will actually be the pre-deployment blood sample taken as a matter of course by the Autralian Army prior to all military deployments.

Bleeding Schedule (all blood samples):

To allow for the analysis of population pharmacokinetics (PK), blood samples will be collected from all study subjects on pre-determined days after dosing on each of the assessment weeks. The pre-determined days will include day 1 (early post-dose, absorption phase), days 3 and 5 (72 – 120 hours post-dose), and day 7 (pre-dose, trough plasma level). Therefore, for example, at week 4, one Company will be bled on day 1, one on day 3, one on day 5 and one on day 7. Thereafter, Companies will be bled in a cyclical fashion such that, at the end of the study, each Company will have been bled on at least one occasion on day 1, 3, 5, or 7. However, the sample on Day 2 of the study (1 – 12 hours post-final loading dose) will be collected from all study subjects.
For further details refer to Appendix D.

ii. Measurement of Parasitaemia

Thick and thin blood films for malaria diagnosis will be obtained from the venous sample (see (i) above) at screening to exclude malaria at the point of entry. Additional smears* will be performed at scheduled visits and on any day a volunteer presents to a medical facility complaining of fever or experiencing any other clinical signs consistent with malaria. All smears will be read initially by the treating facility and then forwarded to AMI for confirmation by a microscopist "blinded" to both study treatment and the previous reader's result. Thick and thin blood films will be stained with Giemsa and evaluated by standard techniques. A total of 200 high-power fields will be viewed before a sample is declared negative. Parasite counts will be expressed per 500 white cell count.

Disagreements between the treating facility reading of the slide and AMI will be adjudicated by a third microscopist. If two microscopists agree that the blood smear is positive, then that volunteer will be classified as a failure of prophylaxis.

If symptoms of malaria are present at the time of diagnosis of malaria, this will be recorded in the CRF.

* Smears will also be performed on any subject who contracts Rickettsia, prior to commencing treatment with doxycycline.

Iii. *Plasmodium* speciation

For positive blood smears (if speciation is not confirmed by light microscopy) *Plasmodium* species will be confirmed using Polymerase Chain Reaction (PCR) techniques. Blood for this test will be obtained from the thick blood smear.

Iv. Plasma drug concentration

On day 2 and weeks 4, 8, 16 and 26, blood samples will be collected for the measurement of plasma drug concentration. From these measurements, SB will characterise the population pharmacokinetics of tafenoquine. In addition, AMI will perform similar measurements on subjects receiving mefloquine only. Steps will be taken to ensure that the study blind is not broken as a result of these measurements.

Plasma for these measurements will come from the samples collected into EDTA for haematology assessments. For full details, refer to Appendix D.

Note: Two additional blood samples will be taken for measurement of plasma drug concentration from any subject diagnosed with malaria during the prophylaxis phase of the study. The first will be at the time of developing parasitaemia and the second 12 weeks later at the subject's final safety follow-up visit. For any subject who develops parasitaemia during the relapse follow-up phase (up to week 12 only) a single sample will be collected at the time of diagnosis.

v. Assessment of Phospholipidosis

All these assessments will be performed on a sample of approximately 100 subjects from the study population.

Diffusion capacity of the lungs to Carbon Monoxide (D_LCO):

D_LCO is a measurement of carbon monoxide (CO) transfer from inspired gas to pulmonary capillary blood. This is a complicated phenomenon involving the distributional relationship of alveolar ventilation to alveolar capillary perfusion, the CO transfer properties at the alveolar capillary interface, haemoglobin concentrations and the reaction rates between CO and haemoglobin. Measuring D_LCO has proved useful in assessing a variety of lung abnormalities and the effects of systemic disease and drugs on the lung. In many disease states the magnitude of abnormalities in D_LCO has been shown to correlate with disease severity.

Measurement will be by a non-invasive "single-breath" technique. This involves a subject exhaling through plastic tubing to residual volume, inspiring a breath of gas mixture (CO and an inert tracer gas), holding the breath then exhaling as a sample of alveolar gas is analysed by the D_LCO machine.

The procedure and calculation takes approximately 5 minutes and for each subject will be repeated three times in succession. An average of these measurements will be determined

and compared to a predicted D_LCO value (calculated using a standard equation correlated to weight, height and sex), with the final result expressed as a percentage of the predicted value.

The first measurement will be performed at the start of the study before dosing commences and the second at the end of the 6 month prophylactic phase.

NOTE: To exclude pre-existing abnormalities, a chest X-ray* and FEV_1 test must be performed prior to the first and second measurements of D_LCO.
*X-ray at study start only required if the subject has not had one in the 4 weeks before study entry.

Eye examination:

A slit lamp examination, along with retinal examination and standard tests of visual field and acuity will be performed at the start of the study during screening and at the end of the 6 month prophylactic phase.

The slit lamp examination involves immobilising the subject's head by resting his chin on a metal bar, and permits a magnified and properly illuminated view of the surface of the eye, eyelids, cornea, retina and associated structures.

Peripheral Blood Lymphocytes:

Two blood samples (5ml EDTA tubes) will be collected from the selected sample of the population under study. The first will be collected at the start of the study before dosing commences and the second at the end of the 6 month prophylactic phase. The tubes containing the whole blood must be centrifuged (within 10 minutes of collection) at 3,000 rpm for 10 minutes.

The plasma must be carefully removed, using a plastic pipette, and discarded, leaving the buffy coat intact.

The tubes should then be topped up with 3% glutaraldehyde in 0.1M cacodylate buffer by pipetting gently down the sides of the tube onto the buffy coat and the packed erythrocytes and allowed to fix for a minimum of 1 hour at room temperature. The fixative must then be renewed and allowed to fix for up to 24 hours. The samples can be stored in a refrigerator at this stage if need be for up to 3 months prior to shipping to the electron microscopy laboratory for assessment of phospholipidosis.

During the study, a total of 10ml whole blood will be collected from each of the subjects involved for this assessment.

vi. Concentration of Methaemoglobin

This procedure will be performed on the same sample of approximately 100 subjects from the study population mentioned in v above.

During the course of the study, two 5ml samples of venous blood will be taken into EDTA tubes for assessment of methaemoglobinaemia.

The first sample will be taken at the start of the study before dosing commences and the second at the end of the 6 month prophylactic phase.

vii. Haematology

Samples for haematology assessments will be taken at screening, day 2 and weeks 4, 8, 16 and 26 of the prophylactic phase.
The following haematology tests will be performed using an auto-analyser, with manual differentiation performed on any abnormal findings:

i. Haemoglobin,
ii. Haematocrit,
iii. Mean Corpuscular Haemoglobin Concentration,
iii. Platelets,
iv. Total White Cell Count,
v. Granulocytes,
vi. Lymphocyte and Monocyte Count.

viii. Biochemistry

Samples for biochemical assessments will be taken at screening, day 2, and weeks 4, 8, 16 and 26 of the prophylactic phase. A sample will also be taken at week 12 of the relapse follow-up phase.

The following biochemical tests will be performed.

i. Creatine Kinase (only at screening, day 2 and end of prophylactic phase)
ii. Urea,
iii. Total Bilirubin,
iv. Aspartate Transaminase
v. Alanine Transaminase
vi. Gamma Glutamyl Transferase
viii Alkaline Phosphatase
ix. Creatinine

ix. G6PD deficiency screening

All subjects will have their G6PD status reconfirmed at screening and compared to their pre-deployment assessment. If no record of the pre-deployment result can be found, an additional G6PD test will be performed using the same screening blood sample (i.e all subjects must have documentary evidence of two G6PD tests prior to study entry). To

enter the study, subjects must be normal on both tests. Subjects with discrepancies between the two results will be excluded from the study and their G6PD status formally reassessed on return to Australia.

x. Pregnancy testing

All female subjects with childbearing potential will be tested for pregnancy at screening and at weeks 4, 8, 16 and 26 by blood testing techniques using standard test kits. Women who believe they have become pregnant or who record a positive result on blood testing will be excluded from the study. (see also section 11(g)).

xi. Electrocardiogram

An ECG measurement will be performed on the group of 100 subjects involved in phospholipidosis and methaemoglobin assessments during the screening period and at week 26. The exact time of the ECG will be recorded in the CRF for later comparison with the time of most recent administration of study medication.

The ECG measurements are performed as part of the safety assessment for analysis of any possible QT effects.

xii. Physical examination

A full physical examination will be performed on study entry, at the end of the prophylactic phase (or on premature withdrawal) and after 12 weeks of the relapse follow-up phase.

d. Detailed Description of Study Visits

Please also refer to the study flow chart at the front of this protocol (see page 4).

i. Screening Log

As soon as a subject is considered for the study, his/her suitability to enter must be assessed by a detailed check of the inclusion and exclusion criteria. If a subject is found not to be suitable, the reason must be clearly stated in the Screening Log (to be provided by SmithKline Beecham).

ii. Subject screening (Day –14 to Day –1)

Prior to a subject's enrollment in the study, he/she must be fully briefed on the aims of the study and what is expected of him/her. The subject must also be given time to study the information sheet before deciding whether or not to take part.

Once the subject has decided to take part in the study, he/she must sign and date the consent form (see Appendix B) before any trial related activity*. The form must then be countersigned and dated by the person involved in the study who took the consent.

The following assessments must then be performed and documented in the case record form (CRF):

- review of inclusion / exclusion criteria
- physical examination
- demographic details (height, weight, gender, age, ethnic origin)
- medical history (including malaria history)
- haematology / biochemistry
- pregnancy test (females only)
- baseline illness, signs and symptoms
- concomitant medication
- phospholipidosis assessments (selected sample only)
- assessment of methaemoglobinaemia (selected sample only)
- ECG (selected sample only)
- blood smear for assessment of parasitaemia
- confirmation of G6PD status

* Note: A blood sample is taken as a matter of course prior to a military deployment. This blood sample will be used as the basis of screening and as the baseline study sample. Therefore, for the purposes of this study, consent is not required from the subject before this sample is taken.
If this sample is taken more than 14 days prior to Day 0, an additional baseline sample must be taken for study purposes.

iii. Day 0 (First dose of study medication)

At this visit, subjects will receive the first dose of the loading dose of study medication (200mg tafenoquine daily for 3 days or 250mg mefloquine daily for 3 days).

The following assessments will be performed and details recorded in the CRF.

- adverse events (to be recorded as baseline signs and symptoms)
- concomitant medication

iv. Day 1

This is the second day of the loading dose regimen.

The following assessments will be performed and details recorded in the CRF.

- adverse events
- concomitant medication

v. Day 2

This is the last day of the loading dose regimen.

The following assessments will be performed and details recorded in the CRF.

- adverse events
- concomitant medication
- haematology / biochemistry
- blood sample for assessment of peak plasma drug concentration*

* Sample to be taken up to 12 hours (range 1 – 12 hours) after last dose of the loading regimen. Plasma for this assay will be taken from the EDTA sample collected for haematology.

After the final dose of the loading dose is taken, the next dose of study medication will be scheduled for day 7 after the first dose of the loading dose regimen. Thereafter, prophylactic medication will be dispensed to subjects on a weekly basis.

vi. Weeks 4, 8 and 16 of prophylactic phase

At each of these visits, the following assessments will be performed and details recorded in the CRF.

- blood smear for parasitaemia
- haematology / biochemistry
- plasma drug concentration
- adverse events
- concomitant medication
- pregnancy test (females only)

For each of these visits, a 'window' of ± 10 days is allowable.
NOTE: For those subjects deployed for more than 6 months due to additional duties, extra visits of this type may be necessary at weeks 24 and/or 28.

vii. Final prophylaxis visit (Week 26 +/- 4weeks)

This visit will occur at week 26 for the majority of subjects. However, due to varied duties, some subjects may be deployed for a shorter or longer period. Therefore, the 'window' for the final prophylaxis visit is 26 +/- 4 weeks.

At this visit, the following assessments will be performed and details recorded in the CRF.

- blood smear for assessment of parasitaemia
- haematology / biochemistry
- plasma drug concentration
- adverse events
- concomitant medication
- pregnancy test (females only)
- physical examination
- phospholipidosis assessments (selected sample only)
- methaemoglobinaemia (selected sample only)
- ECG (selected sample only)

All assessments at this visit will be performed whilst subjects are in barracks in Australia after return from deployment. The phopholipidosis assessments are not likely to be performed at the same time as the other assessments in this visit.

viii. Week 6 of relapse follow-up phase

This visit will be performed in barracks in Australia, after subjects return from leave. At this visit, the following assessments will be performed and details recorded in the CRF.

- adverse events
- concomitant medication
- malaria status

NOTE: In the period leading up to this visit, additional blood samples may be collected for safety purposes if considered necessary by an investigator or co-investigator. All results will be recorded in the CRF.
Any subjects who have symptoms of malaria or who have been diagnosed with malaria will have blood smears taken (see section 7c, General Instructions, page 20). Full details will be recorded in the CRF.

For this visit, a 'window' of ± 2 weeks is allowable.

ix. Week 12 of relapse follow-up phase

This visit will be performed in barracks in Australia, and is timed to coincide with the standard military post-deployment follow-up. At this visit, the following assessments will be performed and details recorded in the CRF.

- physical examination
- biochemistry
- pregnancy test (females only)
- adverse events
- concomitant medication
- malaria status

NOTE: In the period leading up to this visit, additional blood samples may be collected for safety purposes if considered necessary by an investigator or co-investigator. All results will be recorded in the CRF.
Any subjects who have symptoms of malaria or who have been diagnosed with malaria will have blood smears taken (see section 7c, General Instructions, page 20). Full details will be recorded in the CRF.

For this visit, a 'window' of ± 2 weeks is allowable.

x. Weeks 18 and 24 of relapse follow-up phase

Subjects will be followed-up by phone at weeks 18 and 24 (± 2 weeks in each case) and questioned on symptoms of malaria. Details will be recorded in the CRF.

Any subjects who have symptoms of malaria or who have been diagnosed with malaria will have blood smears taken (see section 7c, General Instructions, page 20). Full details will be recorded in the CRF.

8. Study Medication and Administration

a. Study Medication

Tafenoquine will be supplied as Swedish Orange, size 1, hard gelatin capsules, each containing tafenoquine 200mg (pure free base). A matched placebo will be identical in external appearance to the active capsules.

Mefloquine and primaquine will be provided as over-encapsulated tablets containing mefloquine 250 mg or primaquine 7.5mg. Matched placebo for mefloquine and primaquine will be identical in external appearance to active capsules. Both active and placebo mefloquine and primaquine will be provided as size DB-AA capsules comprising an opaque Swedish Orange body and cap.

During the eradication phase, the tafenoquine and mefloquine groups will take either primaquine (15mg base b.d) or placebo alone for a further 2 weeks. Subjects randomised to mefloquine will receive active primaquine whereas those who received tafenoquine will receive placebo primaquine to match.

Sufficient medication will be supplied for each patient to allow for 33 weeks (3 loading doses, plus 32 weekly doses) of prophylactic medication (i.e. tafenoquine or mefloquine), plus overage for losses. For the eradication phase, each patient will be supplied with enough medication (primaquine or placebo) for 14 days, plus overage for losses.

b. Dosage and Administration

On days 0 to 2 of the study, subjects will receive (with food) a loading dose of study medication (tafenoquine 200mg per day for 3 days or mefloquine 250mg per day for 3 days) followed by

weekly doses (again with food) of 200mg tafenoquine or 250mg mefloquine for the duration of the prophylactic phase.

At the end of the prophylactic phase, all subjects will receive primaquine 15 mg or placebo twice daily for 14 days.

If a subject vomits following dosing, the study drug can be re-administered the same or the following day. If a subject sequentially vomits two doses of study medication he/she will be considered intolerant to study medication and be withdrawn from the study.

c. Blinding

This will be a double-blinded, double dummy, study (except the eradication phase which will be single dummy) and all packaging will maintain the double-blind nature of the study.

A subject's randomisation number will define the medication that subject receives. SB will produce code break envelopes for each subject which should only be opened in an emergency (see section 11(h)). Copies of the code break envelopes will be held by the Investigator and by SB. SB will also maintain a master randomisation list.

d. Packaging

The medication will be provided in foil blister packs. Medication numbers will be allocated to 6 strata (stratified randomisation). There will be 4 strata each with 120 medication numbers, one stratum with 112 medication numbers and 1 stratum with 160 medication numbers.

e. Labeling and Preparation

The blisters will be labeled with a small plain white label.

The blister packs may be contained in a small carton, labeled with a small label with a tear-off portion, which constitutes the patient pack.

The label text will include the following information:

- Job Number
- Protocol Number
- Medication Number
- Contents: i.e. quantity and description of dose form.
- Dosage Directions i.e. 'As directed'.
- Storage instructions
- "Keep out of reach of children"
- "FOR CLINICAL TRIAL USE ONLY"
- The sponsor address
- Any other information required by the regulatory authorities in the participating country.

In addition, the text may include the following: regimental no., name and rank to enable the relevant information to be recorded. These details will, however, be removed from any medication or packaging that may be returned to the SB local office.

f. Storage

All study medication will be protected from light and moisture and stored between 15 and 30°C. (The upper temperature limit will be subject to availability of stability data for primaquine over-encapsulated tablets).

All drug supplies will be kept by the Platoon Sergeant in a locked container at the study site. The Platoon Sgt has no medical qualifications above first aid training.

Medications will be stored by AMI with only 4 weeks supply at a time being released forward for each volunteer, under the control of the Platoon Sergeant. In Company base areas and Headquarters rear areas this function will be performed by Medics and Regimental Aid Post staff. AMI staff will undertake roving monitoring each week and weekly checks will be conducted for all volunteers by AMI staff.

g. Drug Accountability

On delivery of the study medication supplies, the investigator or his delegated representative must sign to confirm receipt. All study medication must only be dispensed to study subjects in accordance with the protocol and any unused medication must be returned to SB at the end of the study.

Drug accountability records must be maintained at the site so that, at the end of the study, it will be possible to reconcile delivery records with those of usage and returned stocks. Any discrepancies must be clearly accounted for in writing. Supplies will be inventoried when received and after the closing of the study. Weekly checking fulfils the requirement for drug accountability records to be maintained throughout the study so that there is a perpetual reconciliation of study supplies.

9. Assessment of Compliance

All prophylactic medication will be given under supervision. For the loading dose and weekly dosing regimen, soldiers will receive their medication at a 'tablet parade' (after a meal). The Platoon Sergeant will record that each subject has/has not received their medication dose in a diary.

If a subject should miss 2 consecutive doses of study medication, he/she will be withdrawn from the study. If a subject should miss 2 non-consecutive doses, the investigator should contact the monitor of the study to discuss whether or not the subject can remain in the prophylactic phase of the study.

During the eradication phase (primaquine 15mg b.d for 2 weeks) it will not be possible to directly observe that medication has been taken. Compliance checks will be limited to counts of tablets returned after this phase.

10. Concomitant Medication / Treatment

All concomitant medication taken during the study must be recorded in the case record form with details of indication, daily dose and dates of administration.

If a volunteer develops an infection requiring treatment with antibiotics, the attending study clinician will, if possible, prescribe an antibiotic without known antimalarial action.

Use of anti-malarial drugs other than the study drug (except doxycycline for treatment of Rickettsia) will lead to withdrawal of the subject from the study(see section 12c).

11. Adverse Experiences

The recording of adverse experiences is an important aspect of study documentation. Detailed guidelines are set out below

a. Eliciting and Documenting Adverse Experiences

It is the responsibility of the investigator to document all adverse experiences which occur during the investigation.

An adverse experience includes any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical study whether associated with the study drug, active comparator or placebo and whether or not considered drug related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the disease under investigation that is not recorded elsewhere in the case record form under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered adverse experiences. Discrete episodes of chronic conditions occurring during a study period should be reported as adverse experiences in order to assess changes in frequency or severity.

Adverse experiences should be documented in terms of a medical diagnosis(es). When this is not possible, the adverse experience should be documented in terms of signs and/or symptoms observed by the investigator or reported by the patient at each study visit.

N.B. Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study should be recorded on the Medical/ Surgical history form within the patient's case report form (CRF).

Adverse experiences which occur after informed consent is obtained, but prior to starting active or randomised treatment, will be documented on the 'Baseline signs and symptoms' report form as instructed by the SB clinical Site Monitor.

All adverse experiences occurring after administration of the first dose of study medication (ie active drug, placebo, comparator drug) and on or before the final visit (week 12 of relapse follow-up phase), must be reported on the Adverse Experience form in the subject's CRF, REGARDLESS OF WHETHER OR NOT THEY ARE CONSIDERED DRUG RELATED.

Serious adverse experiences which occur during the clinical study or within 12 weeks of receiving the last dose of study medication, whether or nor related to study drug, must be reported.

Instances of death, cancer or congenital abnormality if brought to the attention of the Investigator AT ANY TIME after cessation of study medication AND considered by the Investigator to be possibly related to study medication, should be reported to SB..

At each visit/assessment, adverse experiences will be evaluated by the Investigator. Adverse experiences not previously documented in the study will be recorded in the adverse experience record form within the patient's CRF. The nature of each experience, date and time (where appropriate) of onset, outcome, course (i.e. intermittent or constant), maximum intensity, action taken with respect to dosage and relationship to treatment should be established. Details of changes to the dosage schedule or any corrective treatment should be recorded on the appropriate pages of the CRF.

Adverse experiences already documented in the CRF ie. at a previous assessment and designated as 'ongoing' should be reviewed at subsequent visits as necessary. If these have resolved, the documentation in the CRF should be completed. NB. If an adverse experience increases in frequency or severity during a study period, a new record of the experience will be started.

As a consistent method of soliciting AEs, ask the subject a non-leading question such as:

"Have you had any problems since starting the new treatment/or since the last visit?"

b. Assessment of Intensity

Maximum intensity should be assigned to one of the following categories:

Mild: An adverse experience which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An adverse experience which is sufficiently discomforting to interfere with normal everyday activities.

Severe: An adverse experience which prevents normal everyday activities.

c. Assessment of Causality

Every effort should be made by the investigator to explain each adverse experience and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories: not related, unlikely, suspected(reasonable possibility), probable.

Not related: The adverse experience is definitely not related to the test drug.

Unlikely: There are other, more likely causes and the drug is not suspected as a cause.

Suspected (reasonable possibility): A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug.

Probable: There probably is a direct cause and effect relationship between the adverse experience and the study drug.

The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of the drug

- Reaction of similar nature being previously observed with this drug or class of drug

- The experience having often been reported in literature for similar drugs as drug related e.g. skin rashes, blood dyscrasia

- The experience being related by time to drug ingestion terminating with drug withdrawal (dechallenge) or reproduced on rechallenge

d. Follow -up of Adverse Experiences

Investigators should follow-up subjects with adverse experiences until the event has subsided (disappeared) or until the condition has stabilised. Reports relative to the subsequent course of an AE noted for any subject must be submitted to SB..

e. Serious Adverse Experiences

Definition of Serious Adverse Experiences:

A serious adverse experience is any event which is fatal, life threatening*, disabling/incapacitating§ or results in hospitalisation**, prolongs a hospital stay or is associated with congenital abnormality, cancer or overdose (either accidental or intentional). In addition any experience which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug will be documented as a serious event.

* Life threatening - definition:

An adverse experience is life threatening if the subject was at immediate risk of death from the event as it occurred; i.e. it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

§ Disabling/incapacitating - definition:

An adverse experience is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

** Hospitalisation:

AEs requiring hospitalisation should be considered serious. Hospitalisation for, e.g, elective surgery which is not the result of an AE (eg elective surgery for a pre-existing condition) need not be considered an AE and should be recorded on the medical/surgical procedures form. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.
In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

Reporting Serious Adverse Experiences:

Any serious adverse experiences which occur at any time during the clinical study or within 12 weeks of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator to the SB Medical Monitor (details below) by facsimile, the preferred method of reporting, or by telephone within 24 hours.

s47F [redacted]

In addition, serious and unexpected adverse experiences must be immediately reported by telephone (and followed up by fax) to:

U.S. Army Medical Research and Materiel Command (USAMRMC)
Deputy Chief of Staff for Regulatory Compliance and Quality
ATTN: MCMR-RCQ,
504 Scott Street,
Fort Detrick,

Maryland 21702-5012.

A written report must follow the initial telephone call within 3 working days and information on the resolution when available. The written report must be addressed to USAMRMC as detailed above.

The Executive Secretary of the Australian Defence Medical Ethics Committee (ADMEC) must be kept informed of all SAEs which occur during the study. Contact details as follows:

Executive Secretary ADMEC
SO1 Medical Standards
DHSB
CP2-7-66

Investigators should not wait to receive additional information to fully document the event before notifying SB, USAMRMC and ADMEC of a serious adverse experience. The SAE form, which should be completed as fully as possible, or the telephone report, should be followed up with a full written summary utilising the SB SAE worksheet detailing relevant aspects of the serious adverse experiences in question. Where applicable, information from relevant hospital case records and autopsy reports should be obtained.

Instances of death, cancer or congenital abnormality if brought to the attention of the Investigator AT ANY TIME after cessation of study medication AND considered by the Investigator to be possibly related to study medication, should be reported to SB and communicated to USAMRMC and ADMEC.

f. Reporting of Overdose

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involves study medication) must be communicated to SmithKline Beecham within 24 hours and be fully documented as a serious adverse experience. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

g. Pregnancy

Subjects who become pregnant during the study should discontinue the study immediately.

Subjects should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within 12 weeks of completing their course of study medication. Such pregnancies should be reported as an SAE to the SB Medical Monitor.

Whenever possible a pregnancy should be followed to term, any premature terminations reported, and the status of the mother and child should be reported to SmithKline Beecham after delivery.

Please see also section 13.

h. Breaking the Study Blind

Only in the event of a serious adverse experience which the investigator feels cannot be adequately treated without knowing the identity of the study medication, may the medication code be broken for a particular subject. Every effort must be made to contact the SB Medical Monitor (see details under section e above) prior to breaking the code.

If this is not possible and the situation is an emergency the investigator may break the code and contact the SB Medical Monitor as soon as possible thereafter.

12. Subject Completion and Withdrawal

a. Definitions

For the prophylactic phase, a completed subject is defined as one who attends visits up to and including the final prophylaxis visit (i.e week 24, 28 or 32), without premature withdrawal (see section (c) below).

For the relapse follow-up phase, a completed subject is defined as one who has had an assessment of their malaria status (as a minimum) at week the 24 visit of the relapse follow-up phase.

b. Procedures for handling withdrawals

If a subject withdraws from the study, as much of the data as possible up to the time of withdrawal must be collected and recorded in the CRF (the Final Prophylaxis visit must be completed where possible). The Study Conclusion page of the CRF must be completed, detailing the reason for withdrawal. If withdrawal is due to an Adverse Event then an Adverse Event Form must be completed. Any subject who withdraws due to an AE will be followed until the AE is resolved.

All subjects who withdraw from the study will be followed up for safety for 12 weeks. Details of assessments during this period will be recorded in the CRF (minimum one visit at 12 weeks post-withdrawal, equivalent to assessments performed at week 12 of the Relapse Follow-up phase).

Any volunteer who withdraws from the study as a result of developing malaria will be treated according to current clinical practice (e.g quinine plus doxycycline for *P.falciparum* infections or chloroquine for *P.vivax* infections).

c. Reasons for withdrawal

Volunteers may withdraw from the study at any time without detriment to their career or medical management. A volunteer may be withdrawn from the study for the following reasons:

- he/she experiences significant adverse reactions to the study medicine, or if concomitant illness is likely to compromise their physical well being or their participation in the study.
- (if female) she becomes pregnant during the study.
- other conditions occur that would make participation or continued drug administration detrimental to their health. These include physical or laboratory evidence of intolerance.
- lack of effectiveness of study medication (i.e contraction of malaria)
- non-compliance with prophylactic study medication (see section 9).
- intolerance to study medication (see section 8(b)).

d. Screening / Baseline failures

Screening books, including the screening conclusion page (where relevant), must be completed for all subjects from whom informed consent is obtained, but who are withdrawn before randomisation. These books must be returned to SB.

13. Pregnancy and Contraception

Female volunteers determined to be non-pregnant on entry to the study will be counselled on contraception. On all subsequent assessments, blood tests will be conducted to determine pregnancy. All volunteers becoming pregnant will be removed from the trial and followed until the conclusion of the pregnancy. Volunteers will be encouraged to continue contraception precautions until twelve weeks after their last dose of study medication.

Please see also section 11g.

14. Data Evaluation

a. Target Sample Size

The primary objective of the study is to compare the safety and tolerability of tafenoquine and mefloquine in a predominantly non-immune Caucasian population. In order to have sufficient numbers of subjects exposed to tafenoquine over a six month period, and to allow comparisons of safety to be made between tafenoquine and mefloquine with a reasonable precision, at least 450 tafenoquine and 150 mefloquine subjects should complete the six month prophylactic phase.

As approximately 5% of subjects randomised are expected to drop out of the study, 632 subjects should be randomised in a 3:1 ratio, with 474 subjects randomised to tafenoquine and 158 to mefloquine.

In the tafenoquine group, the sample size of 474 subjects has a 95% probability of observing at least 1 adverse event for those events that occur at 0.63% or greater. In the mefloquine group, the sample size of 158 subjects has a 95% probability of observing at least 1 adverse event for those events that occur at 1.9% or greater.

The following table gives and idea of the precision with which differences in AEs between treatments can be estimated, with 474 subjects on tafenoquine and 158 on mefloquine:

AE Rate on Tafenoquine	AE Rate on Mefloquine	Difference in Rates	95% Confidence Interval
5%	10%	-5%	± 5.1%
5%	15%	-10%	± 5.9%
10%	5%	5%	± 4.3%
10%	15%	-5%	± 6.2%
15%	5%	10%	± 4.7%
15%	10%	5%	± 5.7%

With 450 subjects on tafenoquine and 150 on mefloquine in the per protocol population, the study has 94% power to detect that the upper limit of the two- sided 95% confidence interval for the difference in failure rates (tafenoquine – mefloquine) at the end of the prophylactic phase is no more than 10%, assuming an underlying failure rate of 10% in each treatment group. This calculation is based on the formula of Makuch and Simon. The table below shows the sensitivity of this under different assumptions :

Failure Rate per Group	Limit of Non-inferiority	Power
10%	10%	94%
10%	7.5%	75%
10%	5%	42%
5%	5%	68%

b. Method of Randomization

All subjects meeting the study criteria will be randomly assigned, in a 3:1 tafenoquine: mefloquine ratio, and in a double-blind fashion, to receive one of the two treatment regimens according to a pre-determined code provided by SmithKline Beecham. The randomisation will be stratified by company. The block size will remain confidential.

c. Breaking the Study Blind

The initial reporting of this study will occur after the first three months of the relapse follow- up phase has been completed for all subjects. All AE data and key efficacy data will have been collected at this time. The only data remaining is information on malaria relapse, collected via telephone, and the investigator will remain blind to treatment at the time of the telephone contact. A SB statistician will be responsible for breaking the blind (once the database is locked) after collection, databasing and cleaning has been completed of all data from the prophylactic phase and first three months of the relapse follow- up and after identification of protocol violators.

d. Planned Efficacy Evaluations

i Endpoints

The primary objective of the study is to assess the safety and tolerability of the two treatment regimens, and conclusions regarding the efficacy of the regimens are difficult without knowledge of the placebo attack rate. However, as a secondary objective is to compare the effectiveness of the two treatments, the following efficacy endpoints will be analysed:

Primary Efficacy Variable:

At the end of the prophylaxis treatment period, the prophylactic outcome for each subject will be derived as follows:

Prophylactic Success: No single positive smear during prophylactic study drug administration (tafenoquine/ mefloquine) up to and including the day of the last dose of eradication medication (placebo/ primaquine).

Prophylactic Failure: Single positive smear during prophylactic study drug administration (tafenoquine/ mefloquine) up to and including the day of the last dose of eradication medication (placebo/ primaquine).

Secondary Efficacy Variables:

The secondary variables are

- number of subjects experiencing malaria at any time during the study
- number of subjects with single positive smear (*P. falciparum* only) during prophylactic study drug administration up to and including the day of the last dose of eradication medication
- number of subjects with single positive smear (*P. vivax* only) during prophylactic study drug administration up to and including the day of the last dose of eradication medication
- time to single positive smear (all species) at any time during the study (prophylactic phase plus 6 months relapse follow- up phase).

Additionally the number of subjects with parasites of species other than *P. falciparum* and *P.vivax*, the number of subjects who test positive at different time points and the number of subjects with symptomatic vs. asymptomatic parasitemia will be summarised.

ii Subject Populations

Two populations will be used for the efficacy analysis:

Intent-To- Treat (ITT) : All subjects who took at least one dose of prophylactic study medication during the prophylaxis treatment period.

Per Protocol (PP): All randomised subjects who satisfied those inclusion/exclusion criteria with the potential to affect efficacy and subsequently adhered to the protocol. This is a subset of the ITT population.

Subjects who receive the wrong coded study medication will be analysed according to the treatment they received.

Subjects will only be excluded from the PP population from the time that the violation occurs. If a subject is a prophylactic failure and then subsequently violates the protocol they will not be excluded from the PP population since they have already satisfied the criteria for failure prior to violation of the protocol.

The ITT population is used to address the question "How does the medication work in subjects who are prescribed the drug and who take at least one dose of the drug?" Subjects will be excluded from the ITT population if there is documented evidence that they have taken no study medication. The PP population is used to address the question "How does the medication work in subjects who are prescribed the medication and who take the medication as prescribed?"

In trials designed to show non- inferiority of a new drug compared to a comparator treatment, the PP population may be thought of as a conservative approach to the statistical analysis. For this reason, the PP population is the population of primary interest for the analysis of effectiveness in this study.

All decisions on eligibility for inclusion in the ITT population will be made prior to code-break or any data evaluation.

e. Methods Of Analysis

i Baseline Characteristics

The baseline demographic characteristics will be summarised to assess the comparability of the treatment groups at baseline. No formal hypothesis testing or interval estimation will be applied to baseline or demographic characteristics.

ii Primary Efficacy Analysis

The primary objective of the study is to compare the safety and tolerability of the two treatments. However, as a secondary consideration, a comparison of effectiveness in the prophylactic phase will be made by calculating a 95% confidence interval stratified by company for the difference in the proportion of prophylactic failures (tafenoquine-mefloquine). A conclusion of non- inferiority of tafenoquine will be drawn if the upper limit of this confidence interval is no more than 10%.

To confirm the appropriateness of using a stratified confidence interval approach an analysis testing for a treatment by company interaction will be performed.

As confirmation of the primary analysis the above will be repeated for the ITT population, and a covariate analysis will be performed.

iii Secondary Efficacy Analysis

For the secondary efficacy variables number of subjects with malaria at any time in the study, number of subjects with a single positive smear (*P. falciparum* only) during the prophylactic phase and number of subjects with a single positive smear (*P. vivax* only) during the prophylactic phase, the 95% stratified confidence interval for treatment difference in proportions as described above will be presented. Again, in each case to confirm the appropriateness of using a stratified confidence interval approach an analysis testing for a treatment by company interaction will be performed.

For time to malaria, a Kaplan- Meier curve will be produced showing the cumulative survival rates for each treatment group.

iv. Interim Analysis

It is planned to set up an independent data monitoring committee (IDMC) to monitor failure rates over the course of the study if required. However no adjustment will be made for multiple comparisons.

The initial reporting of this study will occur at the end of the first twelve weeks of the relapse follow- up phase, with the remaining data on malaria relapse in the last three months being reported at a subsequent timepoint, since all subjects will be analysed at the end of the relapse follow- up phase. However this is not a formal interim analysis and consequently no adjustment of the alpha level will be made.

f. Planned Safety Evaluations

There is one population defined for safety analysis in this study:

Safety: All subjects who took at least one dose of prophylactic study medication (tafenoquine/ mefloquine).

Subjects who receive the wrong study medication will be analysed according to the medication they received.

Summaries of safety data will be produced. Counting will be based on the number of subjects, not the number of AEs e.g. if a subject reports the same AE on three occasions within a time interval, that AE will only be counted once.

For frequently occurring AEs (≥ 5% or 10% subjects in either treatment group - to be decided according to the number of AEs occurring at these levels) the proportion of subjects reporting the AE will be compared between treatments using Fisher's exact test, and two-sided 95% confidence intervals will be used to estimate the difference in proportions between treatment groups.

g. Pharmacokinetic Analysis

Plasma concentration-time data for tafenoquine will be tabulated and plotted for each subject. Population pharmacokinetics (PK) and/or Bayesian estimation methods will be performed using software such as NONMEM or other currently acceptable methods to assess the pharmacokinetics of tafenoquine, if data are appropriate. To support the population PK analysis, the data from this study may be combined with data from other studies. Mean population parameters will be assessed taking into account demographic variables (such as age, weight, gender, race), concomitant medications and/or co-morbid diseases. If data permit, the relationship between tafenoquine concentrations and efficacy parameters and selected adverse events will be explored. Pharmacokinetic analysis of tafenoquine samples will be the responsibility of the Department of Pharmacokinetics, DMPK, SmithKline Beecham. All pharmacokinetic data will be stored in the Archives, SmithKline Beecham, Research and Development. The pharmacokinetic analysis may be reported separately.

Drug and population pharmacokinetic analysis of mefloquine will be the responsibility of the Australian Army Malaria Institute, Brisbane.

15. Administrative Matters

a. Responsibilities of the Investigator

- To ensure that he/she has sufficient time to conduct and complete the study and has adequate staff and appropriate facilities which are available for the duration of the study and to ensure that other studies do not divert essential subjects or facilities away from the study at hand.

- To submit an up-to-date curriculum vitae and other credentials (e.g. medical license number in the United States) to the sponsor and, where required, to relevant authorities.

- To acquire the normal ranges for laboratory tests performed locally and, if required by local regulations, obtain the Laboratory Licence or Certification.

- To prepare and maintain adequate case histories designed to record observations and other data pertinent to the study.

b. Protocol Amendments

No changes to the study protocol will be allowed unless discussed in detail with SB/USAMRMC and filed as an amendment/modification to this protocol.

Any amendment/modification to the protocol will be adhered to by the participating centre (or all participating centres) and will apply to all subjects following approval as appropriate by the Ethical Review Committee or Institutional Review Board.

c. Sponsor's Termination of Study

SB/USAMRMC reserve the right to discontinue the clinical study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be tendered.

d. Case Report Form Instructions

Prior to screening the first potential participant, the investigator will provide a list showing the signature and handwritten initials of all individuals authorised to make or change entries on case report forms (CRFs). If the authorised individuals should change during the study, the investigator is to inform SB.

CRFs will be supplied by SB for recording all data. It is the responsibility of the investigator or co-investigator to ensure that CRFs (and subject diary cards) are legible and completely filled in with a black ink ballpoint pen. Enter the subject's identification (2-3 alphabetic letters representing the subject's initials or first 2-3 letter of subject's first or last name), the patient identification (PID) if not already pre-printed and the visit date, on the CRF Page Headers as required.

Errors must be corrected by drawing a single line through the incorrect entry and writing in the new value/data positioned as close to the original as possible. The correction must then be initialled, dated and justified by the authorised individual making the change. Do not obliterate, write over, or erase the original entry when making a correction.

When a subject completes a visit, it is anticipated that relevant sections of the CRF will be completed by the investigator (or designated staff) within 24 hours of the last data becoming available, but in no case later than 5 days. Similarly, when a subject completes a study, it is anticipated that all relevant CRF pages will be completed within 24 hours of the last data becoming available, but in no case later than 5 days. This also applies to forms for potential study participants who were not randomised to a treatment group.

As soon as the subject has completed/withdrawn from the study and the CRF is completed the principal investigator or designated physician(s) under his/her supervision will sign the study conclusion page of the CRF to confirm that they have reviewed the data and that the data are completed and accurate. If sections of a CRF are to be brought into SB prior to study conclusion, a section conclusion signature is required.

An original (top copy) CRF must be submitted for all subjects who have undergone protocol specific procedures, whether or not the subject completed the study.

While completed CRFs will be reviewed by an SB/USAMRMC professional monitor at the study site, errors detected by subsequent in-house CRF review may necessitate clarification or correction of errors and documentation and approval by the investigator.

Any questions or comments related to the CRF should be directed to the assigned Site Monitor.

e. Monitoring by SmithKline Beecham / USAMRMC

Monitoring visits by a professional representative of the sponsor will be scheduled to take place before entry of the first subject, during the study at appropriate intervals and after the last subject is completed.

Monitoring responsibilities for this protocol will be performed by USAMRMC's Quality Assurance Office and SmithKline Beecham. A Pre-Study/Initiation visit will be conducted with monitors from USAMRMC and SmithKline Beecham. A minimum of two periodic monitoring visits will be conducted. At least one of these visits will be conducted by USAMRMC's Quality Assurance Office and the rest will be conducted by monitors from SmithKline Beecham. The Close-Out monitoring visit will be conducted by monitors from both USAMRMC's Quality Assurance Office and SmithKline Beecham. Monitoring Reports will be provided to USAMRMC's Quality Assurance Office and SmithKline Beecham after each monitoring visit.

These visits are for the purpose of confirming that studies are being conducted in compliance with the relevant Good Clinical Practice regulations/ guidelines, verifying adherence to the protocol and the completeness and exactness of data entered on the CRF and Drug Inventory Forms. The monitor will verify CRF entries by comparing them with the hospital/clinic/office records which will be made available for this purpose. The monitor will retrieve completed CRF sections at each visit. Adequate time and space for these visits must be made available by the investigator.

The investigator must ensure provision of reasonable space and adequate qualified personnel for monitoring visits.

f. Archiving of Data

The investigator must retain subject records and CRFs as well as drug disposition records in an easily retrievable form for the period defined by ICH GCP. Archiving by an independent body can be arranged by SB on behalf of the investigator if necessary. The investigator must have a 'key' linking the subject's identification code (i.e. treatment number) to the subject's clinical file. If the investigator moves or retires, he/she must nominate someone in writing to be responsible for record keeping. Archived data may be held on microfiche or electronic record, provided that a back-up exists and a hard copy can be obtained from it if required.

It is the policy of the U.S Army Medical Research and Materiel Command (USAMRMC) that data sheets are to be completed on all volunteers participating in research for entry into the Command's Volunteer Registry Database. This is a confidential database and the data entered include name, address, social security number (or equivalent) and details of the clinical trial. This information is needed to answer questions concerning subjects participating in research

sponsored by USAMRMC, and to ensure that subjects can be contacted if there is new information on the study drug. The information should be stored for 75 years.

SB agrees to retain its copy of the protocol, approvals and all other documents related to the study, including certificates relating to any audit or inspection procedures carried out by SB.

g. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for SB or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an investigator signs the protocol, he agrees to allow the Drug Regulatory Agency and SB auditors to inspect his/her study records. Furthermore, if an investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application.

SB has a substantial investment in clinical studies. Having the highest quality data and studies are essential aspects of drug development. SB has Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that SB sponsored studies are in accordance with the relevant Good Clinical Practices regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take 1 to 2 days. The SB audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on drug accountability. The SB audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring SB of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- ERC/IRB approval
- Medication accountability
- Approved study protocol and amendments
- Informed consent of the subjects (written or witnessed oral consent)
- Medical records supportive of CRF data
- Reports to the ERC/IRB and the sponsor
- Record retention

SB will gladly help investigators prepare for an inspection.

h. Confidentiality and Publication

The investigator(s) agrees that all information communicated to him by SB/USAMRMC (hereinafter referred to as the sponsor) is the exclusive property of the sponsor and he will

ensure that the same shall be kept strictly confidential by him or any other person connected with the work and shall not be disclosed by him or such person to any third party without the prior written consent of the sponsor. The investigator(s) shall communicate the results of the work promptly to the sponsor.

The sponsor agrees that the investigator(s) shall have the right to publish or permit the publication of any information or material relating to or arising out of the work after prior submission to us provided that, if the sponsor so request, the investigator will delay publication for a maximum of six months to enable the sponsor to protect their rights in such information or material. Any proposed publication or presentation (e.g. manuscript, abstract or poster) for submission to a journal or scientific meeting, should be sent to the sponsor prior to submission, together with confirmation that any other author(s) has seen and agreed the proposed publication/presentation. The sponsor will undertake to comment on such documents within four weeks.

All rights and interests worldwide in any inventions, know-how or other intellectual or industrial property rights which arise as a result of the clinical study which is the subject of this Protocol or which otherwise arise from the information or materials supplied under this Agreement, shall be assigned to, vest in and remain the property of SmithKline Beecham plc and USAMRMC.

16. Signature of Principal Investigators

We have read and understood this study protocol and agree to conduct the study as outlined herein.

_____ Date:

LTCOL Peter Nasveld MBBS BScMed (Hons)

_____ Date:

LTCOL Mike Edstein PhD

Appendix A

World Medical Association
DECLARATION OF HELSINKI
Recommendations Guiding Physicians
in Biomedical Research Involving Human Subjects
Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly Tokyo, Japan, October 1975
35th World Medical Assembly Venice, Italy, October 1983
41st World Medical Assembly Hong Kong, September 1989
and the
48th General Assembly Somerset West, Republic of South Africa, October 1996.

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research. Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interest of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity make it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any – should be assured of the best-proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission the independent committee (see I,2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers -- either healthy persons or volunteers for whom the experimental design is not related to the patient's illness.
3. The investigator of the investigation team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

APPENDIX B

INFORMATION SHEET

A randomised, double-blind comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor

Principal Investigators:
LtCol Peter Nasveld, MBBS, BScMED, FACRRM
LtCol Mike Edstein, PhD

Protocol No.
SB 252263/033 (ADMEC 216/00)

You have been asked to take part in this research study. The purpose of this form is to explain this research study to you and to obtain your consent to take part in this study.

PURPOSE OF THE STUDY

Because you are deploying to an area where Malaria is known to occur, the decision has been taken by Land Command Health Services to provide you with drugs to protect you against this potentially life-threatening disease. The purpose of this study is to look at the safety and effectiveness of a new drug, ***tafenoquine***, for the prevention of malaria. We also wish to compare tafenoquine with another drug, ***mefloquine***, which has been widely used over the past decade and is one of the alternative drugs currently used by the ADF to prevent malaria.

WHAT IS THE MEDICINE?

If you agree to take part in the study, you will be assigned at random to one of two treatment groups. The study will be "***double-blinded***" which means that neither you nor your doctor will be aware which medication you are taking. You will receive either one tafenoquine (200mg) capsule each day for three consecutive days during pre-deployment training followed by one tafenoquine capsule weekly throughout the deployment or one mefloquine (250mg) capsule each day for three consecutive days during pre-deployment training followed by one mefloquine capsule weekly throughout the deployment. You will have a 75% chance of being on tafenoquine and a 25% chance of being on mefloquine. You will take all medication with food to reduce side effects. The doses will be issued to you weekly so we can accurately record when you have taken your medication.

When you return to Australia, you will undergo treatment to get rid of any malaria parasites that may have collected in your liver. Those who received mefloquine will be given the standard drug used for this purpose called primaquine. You will take one capsule (15mg) twice a day for 14 days. If you received tafenoquine, this eradication course is not necessary, therefore you will take one capsule of placebo twice a day for

Witness Initials_____ Subject initials _____

[redacted]

14 days. As before, you will not know which treatment you are taking, but you will have a 75% chance of receiving placebo and a 25% chance of receiving primaquine.

While tafenoquine has been given to several thousand individuals safely (including more than 1,000 ADF personnel during trials in Bougainville and East Timor), it has not yet been registered with the regulatory authorities in Australia or the USA. Consequently it is still defined as an "experimental" compound.

WHAT IS THE STUDY?

The study involves up to 700 volunteers receiving tafenoquine or mefloquine weekly throughout the deployment. Should you develop a fever within 12 months of returning home, you are asked to attend your local health facility and show them your study ID card. This ID card will contain details on how you should be investigated, how to contact the investigators, and how you should be treated if malaria is diagnosed.

LENGTH OF THE STUDY

The study will begin during pre-deployment training in Townsville, continue during the deployment, with follow-up until 6 months after your deployment is completed. Your only involvement after redeployment will be normal follow-up (after 6 and 12 weeks) by your RAP according to LHQ directives, plus telephone interviews at 18 and 24 weeks after returning to Australia. Should you get malaria after this, your Doctor or RAP will undertake normal reporting to AMI. There are no additional blood tests during the follow-up period over those normally required for personnel re-deploying from overseas service.

STUDY TESTS

As the investigators are looking at drug levels in your blood, checking your blood for malaria and measuring biochemical (liver and kidney function) and haematological (blood cell) levels in your blood to monitor safety, you will be requested to provide samples of blood from your arm. These tests involve the drawing of 9mls (two teaspoons) of blood on up to 9 occasions. Three (3) of these samples would be required anyway as part of your deployment requirements as directed by LHQ. Over the course of the study, a total of 81mls of blood will be collected.

A selected Company sized group will also have additional tests (including chest X-ray and ECG) done to look at other effects that either of the study drugs may have, as well as having eye and lung function tests done before and after the deployment. This will require an additional 20 mls of blood to be taken.

Female volunteers will have pregnancy testing performed on their blood samples on all occasions that blood is taken. No additional blood will be taken for this purpose.

RISKS / DISCOMFORTS

There may be some bruising with blood taken from the veins in your arm.

Tafenoquine has a risk of producing a bleeding disorder if given to people who lack a particular enzyme called G6PD. You have been tested for this enzyme prior to deployment, and will not receive either drug if you have this deficiency. In eight previous clinical trials involving human subjects, including studies in ADF personnel on Bougainville, tafenoquine was noted to produce nausea, vomiting and diarrhoea in some subjects (usually self limiting and improved by taking the medication with food) and mild headache. Similar side effects are seen with mefloquine. In addition, mefloquine has also rarely (about 1:10,000) been associated with depression and anxiety. Both tafenoquine and mefloquine are considered to be safe, however, neither are recommended for use in pregnant females. Primaquine has similar side-effects to tafenoquine including the risk of producing the bleeding disorder related to a lack of G6PD, as described above.

Although you will be taking study medication designed to prevent malaria, there is a very small chance that you may contract malaria while on the study. However, if you do contract malaria you will be treated by your company medic or study investigator and followed up until you are better.

BENEFITS

The benefit of taking part in the study is that you will be more closely monitored for the development of malaria during and after your deployment. You will be taking a medication once weekly rather than once daily with the ADF standard drug, doxycycline. In addition, the study results may provide a better understanding on how to prevent malaria infection on future overseas deployments.

PRECAUTIONS

If you have had a significant response to any medications in the past, or have experienced urticaria (hives) or anaphylaxis (a significant allergic reaction involving collapse, swelling of the face and mouth, difficulty breathing) you may not be able to take part in the study. If you have experienced this type of reaction, please discuss this with the study Medical Officer.

Pregnancy - If you think (females only) that you may be pregnant or intend to become pregnant within one month of returning to Australia, please discuss this with the study Medical Officer. It is recommended not to become pregnant within 3 months of ceasing the medication.

Contraception – While taking this medication, it is recommended that females use an accepted form of contraception*, which may include abstaining, barrier methods or pharmaceutical methods ("the pill"). Tafenoquine and mefloquine are not considered to interact with Oral Contraceptive Pills. If you are concerned about such interactions or have any questions about contraception while on the medication, please discuss this

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Witness initials_____ Subject initials _____

with the study Medical Officer. Continue precautions for 3 months after stopping treatment.
*It should be remembered that no barrier or pharmaceutical method of contraception is 100% effective.

CONFIDENTIALITY

In all reports, publications or presentations about this research, information about you and your participation in this study will be kept in the strictest confidence and will not be released in any form that personally identifies you (a study number only will be used). The investigators will have your contact details and full name to allow them to make sure you can be contacted if necessary. This information will not be passed on to anyone else. Your medical records will be kept confidential and only released to medical personnel to assist in any care that you may need. Your name will not appear on any reports about this study.

From time to time a monitor representing the sponsors of the study (SmithKline Beecham / US Army Medical Research and Materiel Command), or a regulatory authority such as the Therapeutic Goods Administration in Australia or the US Food and Drug Administration, may require access to your medical records to ensure that the study is being carried out to the international standards under Good Clinical Practice (GCP). This access will be supervised by one of the study team and all monitors are bound by a confidentiality agreement.

It is the policy of the USAMRMC that data sheets are to be completed on all volunteers participating in research for entry into the Command's Volunteer Registry Database. This is a confidential database and the data entered include name, address, social security number (or equivalent) and details of the clinical trial. This information is needed to answer questions concerning subjects participating in research sponsored by USAMRMC, and to ensure that subjects can be contacted if there is new information on the study drug. The information will be stored for 75 years.

COMPENSATION

All necessary medical care for injury or disease caused by your participation in this study will be provided at no cost to yourself. Compensation other than medical care will be provided according to the compensation provided as a member of the Australian Army. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study. Should you consider injury or illness has resulted from your participation in the study, you should seek immediate assistance from your nearest medical facility. The study investigators may be advised by calling the pager number on your study ID card.

YOUR RIGHTS

If during the course of the study you have any questions, or believe you have sustained a research-related injury or illness you can contact the study investigators, or your medical facility. Additionally, any concerns can be raised with the Executive Secretary of the Australian Defence Medical Ethics Committee as detailed below:

Executive Secretary
Australian Defence Medical Ethics Committee
CP2-7-66
Department of Defence
Canberra, ACT, 2600

INVESTIGATOR RESPONSIBILITIES

The investigators are responsible for ensuring that the study is conducted according to accepted Good Clinical Practice (GCP) standards, and for ensuring that the well being of study participants is always considered over all other considerations. Additionally, they are required to advise you in a timely manner should any other information become available that may be relevant to your willingness to participate in the study.

YOUR RESPONSIBILITIES

Should you agree to enter the study, you should be prepared to undertake all doses of drug required during the deployment, as well as all tests and follow-up required. Should you experience any medical problems, including suspected side effects to the study drugs, you should report these promptly to your Company medic, RAP or study investigator. If you want any further information on the study, please contact the study investigator named on the attached consent form.

VOLUNTARY PARTICIPATION

Your decision to participate in this study is entirely voluntary and refusal to participate will involve no penalty or loss of benefits to which you might otherwise have been entitled. Should you choose to be omitted from the study, or to withdraw from the study at any stage, there will be no detriment to your medical care or your career. If you choose to leave the study you should advise the study investigators. The study doctor has the right to withdraw you from the study if he/she feels it is appropriate to do so. This will be done if he/she feels that it is not in your best interest to continue either because of side effects of the drugs, or other injuries or illnesses you may experience during the deployment.

Should you not wish to participate in the study, you will require:
a) the normal prevention course for malaria of **doxycycline daily** during the deployment,

b) a malaria eradication course on returning to Australia including:
   i) two weeks of **doxycycline daily** and
   ii) two weeks of **primaquine three times a day**, and

c) all the required **blood samples** taken for deployment and post deployment screening.

SB 252263/033

Volunteer ID: _____

INFORMED WRITTEN CONSENT

I have carefully read the information provided to me in this information sheet (dated.....). All questions raised by me have been answered to my satisfaction. I have been given a copy of this Information Sheet and Consent Form. I understand that I am free to withdraw from the study at any time without incurring any disadvantage to me in the future.

I consent to my participation in the study

VOLUNTEER'S SIGNATURE _____

Printed Name: _____

Date: _____

INVESTIGATOR'S SIGNATURE _____

Printed Name: _____

Date: _____

WITNESS SIGNATURE _____

Printed Name: _____

Date: _____

ADDRESS OF SUBJECT: Lavarack Barracks, Townsville, Queensland, Australia.

APPENDIX C

Pharmacokinetic Sampling

Sample Collection

Blood samples will be collected from subjects for pharmacokinetic analysis during the double blind phase, and should include the time points detailed in the table below. These samples may be limited to selected companies of troops. Three post-dose samples will be collected within varying time windows, as follows: 1-12 hours following administration of the third loading dose, 1 – 12 - hours post-dose , and 72-120 hours (3-5 days) post-dose.. In addition, trough samples will be collected prior to dosing of study medication. The timing of blood draws for safety will be adjusted to fit in with PK sampling.

Although the logistics of drawing blood from large numbers of subjects in the study environment may not allow, the proposed sampling schedule is as follows (to allow for data from this study to be combined with data from other studies in the phase III programme)

Post third loading dose (1-12 h)	Wk 4 pre-dose	Wk 8 1-12 h post dose	Wk 16 3-5 days post-dose	Wk 26 pre-dose
X	X	X	X	X

However, samples will be collected from all subjects at the specified times above relative to dosing, but not necessarily on the assessment weeks specified above (see section 7(c)(i), 'Bleeding Schedule(all blood samples)').

In addition, two samples will be collected from each subject who develops parasitaemia during the prophylactic phase: one at the time of developing parasitaemia, and the second 12 weeks later.

No. of subjects	Time of parasitemia	Week 12 follow-up
Any with parasitemia	X	X

NOTE: For any subject who develops parasitaemia during the relapse follow-up phase (up to week 12 only) a single sample will be collected at the time of diagnosis.

If possible, sampling times within a particular window should be spread across that window rather than being grouped at extreme ends of the window (e.g. 1-12 h window - not all samples at 6 h). The **date and exact** time of each sample should be recorded on the CRF. The **exact** date and time of administration of the dose prior to the sample collection must also be recorded in the

CRF (note: for the loading dose regimen, the exact date and time of all 3 doses should be recorded).

Blood Sample Preparation

Blood samples (2.5 ml) will be collected into EDTA tubes and stored at 4°C in a portable fridge until centrifuged. Plasma will be separated by centrifugation and will be transferred to appropriately labeled polypropylene tubes. Plasma samples will be stored frozen at approximately -20°C or colder until shipped to either Department of Drug Analysis, SmithKline Beecham, The Frythe, UK or its designee. SB or its designee will store (-20°C or colder) the frozen pharmacokinetic plasma samples until analyzed for tafenoquine concentrations using an approved assay technique. Samples should be shipped intermittently during the study period.

Drug Analysis

Plasma concentrations of tafenoquine will be determined by SB or its designee using approved assay methodology for the quantification of tafenoquine in human plasma. The drug analysis aspects of this study will be done under the direction of the Department of Drug Analysis, DMPK, SmithKline Beecham Pharmaceuticals, UK. The randomization treatment code may be provided to the Drug Analysis Department in order to avoid analyzing samples from patients receiving the active comparator. Prior to database freeze, this information will not be communicated to anyone outside DMPK, SmithKline Beecham Pharmaceuticals. All drug analysis data will be stored in the Archives, SmithKline Beecham, Research and Development or its designee.

Pharmacokinetic Analysis

Plasma concentration-time data for tafenoquine will be tabulated and plotted for each subject. Population PK and/or Bayesian estimation methods will be performed using software such as NONMEM or other currently acceptable methods to assess the pharmacokinetics of tafenoquine, if data are appropriate. To support the population PK analysis, the data from this study may be combined with data from other studies. Mean population parameters will be assessed taking into account demographic variables (such as age, weight, gender, race), concomitant medications and/or comorbid diseases. If data permit, the relationship between tafenoquine concentrations and efficacy parameters and selected adverse events will be explored.
Pharmacokinetic analysis of tafenoquine samples will be the responsibility of the Department of Pharmacokinetics, DMPK, SmithKline Beecham. All tafenoquine pharmacokinetic data will be stored in the Archives, SmithKline Beecham, Research and Development. The pharmacokinetic analysis may be reported separately.

Drug and population pharmacokinetic analysis of mefloquine samples will be the responsibility of the Australian Army Malaria Institute, Brisbane.

APPENDIX D

References:

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04/11/2000 15:52 +61-747282498 LB&MJ BRENNAN; PAGE 01

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LTCOL Brennan Senior
Medical Officer
Headquarters 3rd Brigade
Lavarack Barracks
Townsville Qld 4813
Australia

To: LCDR Blenkin Executive Secretary, ADMEC

s47F SB Medical Monitor, SB Singapore

Deputy COS for Regulatory Compliance and Quality, Attn. MCMR-RCQ, USAMRMC

From: [redacted] Pages: 7

Phone: Date: 11/03/00

Re: ADMEC No. 216/00 CC: [Click here a

SB 252263/033

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

• Comments:

Please find enclosed the Preliminary Serious Adverse Event Reports for three recent admission from the 1 RAR Gp into the UN Hospital – Dili. Completed forms will be sent when additional information available.

s47F [redacted]

Page 1

Centre Number	Subject	Subject Initials
	s47F	

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE LTCOL BRENNAN
(Please print clearly)

Serious Adverse Experience *(Please print clearly)*	Bilateral Ingrown Toenails (Great/1st) Toes
Onset Date and Time	01 NOV 04 UG (Day Month Yr 24hr:min)
End Date and Time *(If ongoing please leave blank)*	(Day Month Yr 24hr:min)
Outcome *If subject died, please complete Form D*	☐ Resolved ☒ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ ☒ Constant
Intensity *(maximum)*	☐ Mild ☒ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☒ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/ restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☒ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section*	☒ Yes ☐ No
Was subject withdrawn due to this specific SAE ?	☐ Yes ☒ No

→ *Specify reason(s) for considering this a serious AE. Mark all that apply.*

[1] ☐ fatal
[2] ☐ life threatening
[3] ☐ disabling/incapacitating
[4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures)
[5] ☐ hospitalisation prolonged
[6] ☐ congenital abnormality
[7] ☐ cancer
[8] ☐ overdose
[9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution

Did the SAE abate? ☒ Yes ☐ No

If study medication was interrupted, stopped or dose reduced:
Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No

If yes, did SAE recur? ☐ Yes ☐ No

→ **Assessment**
The SAE is probably associated with:

☐ Protocol design or procedures (but not to study drug)
Please specify _____

☒ Another condition (eg, condition under study, intercurrent illness)
Please specify Ingrown toe nails

☐ Another drug
Please specify _____

2 of 7

Page 1

Centre Number	Subject Number	Subject Initials
		s47F

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE Lt Col BRENNAN
(Please print clearly)

Serious Adverse Experience
(Please print clearly): Upper Abdominal pain

→ *Specify reason(s) for considering this a serious AE. Mark all that apply*

- [1] ☐ fatal
- [2] ☐ life threatening
- [3] ☐ disabling/incapacitating
- [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures)
- [5] ☐ hospitalisation prolonged
- [6] ☐ congenital abnormality
- [7] ☐ cancer
- [8] ☐ overdose
- [9] ☐ investigator considers serious or a significant hazard, contraindication, side effect or precaution

Onset Date and Time: 02 NOV 00 N/A
Day Month Yr 24hr:min

End Date and Time
(If ongoing please leave blank)
Day Month Yr 24hr:min

Outcome
If subject died, please complete Form D ←
- ☐ Resolved
- ☒ Ongoing
- ☐ Died

Experience Course
- ☐ Intermittent → No. of episodes ☐
- ☒ Constant

Intensity *(maximum)*
- ☐ Mild
- ☒ Moderate
- ☐ Severe

Action Taken with Respect to Investigational Drug
- ☒ None
- ☐ Dose reduced
- ☐ Dose increased
- ☐ Drug interrupted/ restarted
- ☐ Drug stopped

Did the SAE abate? ☐ Yes ☒ No

If study medication was interrupted, stopped or dose reduced:
Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No

If yes, did SAE recur? ☐ Yes ☐ No

Relationship to Investigational Drug
- ☐ Not related
- ☐ Unlikely
- ☒ Suspected (reasonable possibility)
- ☐ Probable

→ **Assessment**
The SAE is probably associated with:
- ☐ Protocol design or procedures (but not to study drug)
  Please specify _____
- ☐ Another condition (eg, condition under study, intercurrent illness)
  Please specify _____
- ☐ Another drug
  Please specify _____

Corrective Therapy
If 'Yes', record details in the Concomitant Medication section ←
- ☒ Yes
- ☐ No

Was subject withdrawn due to this specific SAE ?
- ☐ Yes
- ☒ No

4 of 7

Centre Number	Subject Number	Subject Initials
		s47F

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
Bilirubin	03 Nov 00 (Day Month Yr)	25		
GGT	03 Nov 00 (Day Month Yr)	9		
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

Admission after 24 hours of upper abdominal pain, investigations ongoing. Medication / CRF not currently available but will be prior to next due dose on Sunday. LFT results unlikely to be clinically significant but will be monitered.

If applicable, was randomisation code broken at investigational site? ☒ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature: ..... **Date** (Day Month Year)
(confirming that the above data are accurate and complete)

Please PRINT Name .....

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Page 1

Centre Number	Subject Number	Subject Initials
		s47F

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE *(Please print clearly)*: LTCOL BRENNAN

Serious Adverse Experience *(Please print clearly)*	Painfull Swollen Testicle
Onset Date and Time	03 NOV 00 (Day Month Yr) N/A (24hr:min)
End Date and Time *(If ongoing please leave blank)*	(Day Month Yr) (24hr:min)
Outcome *If subject died, please complete Form D*	☐ Resolved ☒ Ongoing ☐ Died
Experience Course	☐ Intermittent → No. of episodes ☐ ☒ Constant
Intensity *(maximum)*	☐ Mild ☒ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug	☒ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/ restarted ☐ Drug stopped
Relationship to Investigational Drug	☐ Not related ☒ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy *If 'Yes', record details in the Concomitant Medication section*	☒ Yes ☐ No
Was subject withdrawn due to this specific SAE ?	☐ Yes ☒ No

→ *Specify reason(s) for considering this a serious AE. Mark all that apply.*

- [1] ☐ fatal
- [2] ☐ life threatening
- [3] ☐ disabling/incapacitating
- [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures)
- [5] ☐ hospitalisation prolonged
- [6] ☐ congenital abnormality
- [7] ☐ cancer
- [8] ☐ overdose
- [9] ☐ investigator considers serious or a significant hazard, contraindication, side effect or precaution

Did the SAE abate? ☐ Yes ☐ No

If study medication was interrupted, stopped or dose reduced:
Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No

If yes, did SAE recur? ☐ Yes ☐ No

→ **Assessment**
The SAE is probably associated with:

☐ Protocol design or procedures (but not to study drug)
Please specify _____

☒ Another condition (eg. condition under study, intercurrent illness)
Please specify Epididymo-orchitis

☐ Another drug
Please specify _____

6 of 7

Page 2

Centre Number	Subject Number	Subject Initials
		s47F

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
WCC	03/Nov/00 (Day Month Yr)			
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Remarks *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

Emergency AME for possible torsion of testies - provisional diagnosis now epidydimoorchitis treated with IV Amoxycycline and doxycycline. Doxycycline treatment will require further assessment by P.I inrelation to continuation on trial. CRF/medication number not available yet. WCC increased

If applicable, was randomisation code broken at investigational site? ☒ No ☐ Yes

Randomisation / Study Medication Number:

Investigator's Signature: ..... **Date** (Day Month Year)
(confirming that the above data are accurate and complete)

Please PRINT Name .....

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Report to ADMEC dated 30 December 2000
SB 225262/033
ADMEC216/00

Background:

Approval was given by ADMEC to conduct the subject trial on 14 June 2000. The subject population consisted of members of the 1st Battalion Group deploying in support of Peace Keeping operations to East Timor. A total of four amendments have been processed and approved by ADMEC. A fifth amendment is lodged concurrently with this report.

Recruitment:

A total of 759 personnel underwent the process of recruitment into the subject trial. Recruitment was conducted in Townsville prior to the deployment of troops into a malarious area and consisted of:

a. A briefing (information session) conducted by the Regimental Medical Officer (Medical Monitor) undertaken 2 weeks prior to the commencement of the formal recruitment process;
b. Secondary group briefings in groups of approximately 30 conducted by an Investigator, where opportunities to clarify issues and concerns was offered along with detailed information on risk and benefit;
c. Further opportunities to clarify issues with an Investigator in groups of 2 individuals prior to obtaining signed informed consent. In each group of 2, one witnessed the obtaining the consent of the other, and vice versa.

Screening:

A total of 663 individuals completed the full consent process and proceeded to the screening phase of the study. This represents a consent rate of 87%. The remainder was recorded as "unable/unwilling to comply with the protocol". This single category was applied to potentially protect individuals from suffering any possible recourse from their decision not to enter the study. In this way they were grouped with others who were not able to comply with the protocol for failing to meet the inclusion/exclusion criteria of the protocol.

The screening total includes potential volunteers who subsequently were excluded for clinical chemistry or haematology parameters outside the inclusion ranges specified in the protocol. As these volunteers were clinically well and had received no trial medication, they are not subject to the followup requirements of the protocol, and have been formally withdrawn.

Enrolment:

A total of 654 volunteers were subsequently commenced on trial medication with a three day loading dose administered under supervision in Townsville. The upper limit for enrolment was 660 so 99% of maximum target was achieved. This allows for up to

60 withdrawals over the prophylaxis phase of 6 months without affecting statistical power calculations.

Of these, 2 volunteers experienced adverse reactions significant enough to warrant removal from the trial during the loading dose phase. One for aggravation of baseline gastrointestinal symptoms and the other for nausea persisting throughout the loading dose. Consequently, 652 commenced the prophylaxis phase proper. The two volunteers withdrawn are being followed up for the 3 month period required by the protocol, and to date have reported no sequelae to their initial inclusion in the study.

Withdrawals:

No volunteers have requested withdrawal from the study since enrolment. In addition to those withdrawn during loading dosing, a further five volunteers have been withdrawn for the following reasons:

a. One for skin rash possibly drug related;
b. One for depression probably drug related;
c. One for gastrointestinal symptoms, probably drug related;
d. One for compassionate reasons (returned to Australia early); and
e. One returned to Australia for ongoing medical treatment for gunshot injuries not related to the trial medication.

Progress:

The study is currently progressing well, with an adverse event rate possibly related to the drug of approximately 3.8% over a minimum of 10 doses per volunteer. This represents a crude estimate as the data is subject to more formal evaluation once data entry has been completed. There have been no significant trends in clinical chemistry or haematological parameters suggesting renal or hepatic toxicity.

As at this date there have been no cases of malaria in Australian troops for the wet season 2000-01. Background rates in the local population have been showing a steady rise over this period, indicating that the parasite is present and increasing.

Serious Adverse Events:

As at 31 December 2000 there had been a total of 23 Serious Adverse Events. In all but one case (gunshot wound) the reason for classification was the process of hospitalisation in the UN Military Hospital, Dili. It is considered that this simple system of classification has led to marked over-reporting on the "serious" category to date. It is anticipated that amendment 5 will reduce the reporting rate by excluding those events which represent admissions for situational rather than clinical indications. Two events were considered to be possibly drug related and in both cases the volunteers have been removed from the study.

Summary:

The trial has been carried out within the guidelines of good clinical practice. The recruitment achieved 99% of target which, when coupled with a lower than anticipated withdrawal rate has ensured maintenance of original power calculations. Specifically, all effort was made to eliminate any suggestion of coercion during the recruitment phase. Preliminary information, while incomplete, would indicate that the trial medication and comparator are both effective and safe.

The prophylaxis phase will be completed over the period 16 April – 2 May 2001, prior to the next scheduled report to ADMEC.

LtCol Peter Nasveld
Principal Investigator

17 January 2001

(1) Serious Adverse Events (SAE) from the use of Tafenoquine in Protocol 216/00 – A Randomised Double Blind Comparative Study to Evaluate the Safety, Tolerability, and Effectiveness of Tafenoquine and Mefloquine for the Prophylaxis of Malaria in Non-Immune Australian Soldiers Deployed to East Timor

6. Major Kitchener addressed ADHREC at length with regard to the SAEs observed in the above study. He referred in particular to the keratopathy resulting in whorls in front of the cornea which have been observed following ophthalmological examination of study subjects. These effects have been found in approximately 75% of the 97 subjects randomly selected for detailed examination. Major Kitchener was unable to confirm whether this proportion related to the 75% of subjects receiving Tafenoquine, as the researchers are blinded to which subjects are receiving Tafenoquine, and which Mefloquine.

7. s47F in particular questioned Major Kitchener as to whether he had any knowledge of the keratopathy having long term manifestations, or whether the keratopathy had ever recurred at a later date, for example years later, following cessation of administration of related drugs. Major Kitchener assured ADHREC that in his extensive research into these questions he had not discovered that either situation had ever arisen.

8. The Chair then asked all AMI members to be excused. Lengthy discussion took place regarding the SAEs above, and the implications for any further use of the drug in the future. The Chair explained to ADHREC that this type of side effect is well known in other drugs of similar type, known as cationic amphiphilic compounds, notably amiodarone, which is used in the treatment of cardiac dysrhythmia. Keratopathy in this case is not regarded as an indication for cessation of treatment, but rather a sign that the patient is taking their medication. Changes are well known to be reversible on cessation of the medication.

9. s47F suggested to ADHREC that an opinion from an independent ophthalmologist be sought to advise Committee of the likely significance of the above findings. In addition, discussion took place as to how long a time period to full or partial resolution of the effects was reasonable. Discussion also took place to the effect that any commencement of further trials involving Tafenoquine could occur until these matters were resolved.

Recommendation:
The meeting resolved to request an independent ophthalmological assessment of the likely effects of keratopathy from the specialist Reserve ophthalmology consultant to the Defence Health Service. ADHREC maintained its position that no further administration of Tafenoquine is to take place in any AMI trials until formal ophthalmological review has shown that keratopathy has completely resolved, or that specialist advice is that it will resolve in the near future. An appropriate time frame for this resolution is to be indicated. This opinion is to be furnished in writing to ADHREC. Formal clearance in writing to AMI to proceed with any use of Tafenoquine will only be given when ADHREC has had the above matters addressed to its satisfaction.

For action:
Chair
Exec Sec

17 September 2001

3. The Chair invited Lieutenant Colonel Peter Nasveld and Lieutenant Commander Sonya Bennett to address ADHREC. Lieutenant Colonel Peter Nasveld reported on the Tafenoquine trial ADHREC Protocol 216/00. Lieutenant Colonel Nasveld reported the following:

(1) Update on SAE status Tafenoquine.

- The trial went well, it was a well-managed trial and the findings were promising.
- Use of other Anti-malarials, in similar personnel in similar environmental conditions had reported 20% vivax malaria at 6 months post-deployment. The trial population had reported only 1% vivax at 6 months post last dose.
- Throughout the operational deployment, no cases of malaria were reported in the trial population, other comparable groups have reported 3-4%.
- Tafenoquine has had a profound efficacy in the treatment of recurring vivax malaria. The findings from this and other trials are identifying Tafenoquine as an important drug for use in ADF and World Health Organisation Malaria programs.
- The adverse event findings were not entirely unexpected although they had not been seen before in animal trials or early clinical trials of Tafenoquine
- No pre-trial assessment or baseline data collection was included in the protocol as there was no cause. There is possible reason to review this now. These investigations are pseudo invasive and are at an increased risk to the subjects.
- Pigmented changes in the eyes have been observed in other drugs of the same class, these changes all regress and resolve.
- The effect is believed to be dose dependent.
- Throughout the trial no reports from subjects were received related to changes in visual perception.
- The eye changes were universal in the Tafenoquine group, only one in the eye examination subset did not have the pigmented whirl in the outer layer of the cornea.
- Of the subset of 100 of the study population who had eye exams, 95 went on to participate in the study, 77 have been followed up. Of this 77, 59 were in the Tafenoquine group. Of this 59, 36 (61%) had complete resolution by 10 weeks post last dose
- The 18 members of the eye examination subset that have not had three-month post last dose follow up will be reviewed between the 8-12 October.
- Consultant ophthalmologists expect complete resolution.
- IND approval from the FDA has been voluntarily suspended by the researchers, the FDA will re-activate the IND approval at the 2/3 mark, that is when 2/3 of the study population have had complete resolution and

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AIR VICE-MARSHAL BRUCE SHORT RFD

THE SURGEON GENERAL
AUSTRALIAN DEFENCE FORCE

Department of Defence
CP2-7-124
Campbell Park Offices
Canberra ACT 2600

21st June 2001

Colonel J.L. Crompton RFD
SGADF Consultant Ophthalmologist
22 Walter Street
North Adelaide SA 5006

Dear John.

At the 43rd Meeting of the Australian Defence Human Research Ethics Committee on the 18th June 2001, the topic of a serious adverse event in a trial using the anti-malarial drug, *Tafenoquine* was discussed.

The researchers reported the occurrence of vortex keratopathy due to phospholipidosis induced by the cationic amphiphile, *Tafenoquine*. The trials of personnel receiving the drug have been subsequently suspended pending further investigations of this asymptomatic keratopathy. Information that a similar corneal deposition is found in patients receiving *Amiodarone* as well as *Chloroquine* was also provided to the committee. Ophthalmological screening of exposed ADF personnel is presently on-going.

The committee resolved that ADHREC seek an independent ophthalmological opinion as to the significance and long term effects, if any, of *Tefanoquine* –induced Keratopathy, and to obtain a report for presentation at the 44th meeting set down for the 17th September 2001.

I would be obliged if you could provide me with such an opinion at your earliest convenience. I will arrange for you to receive all the relevant documentation about the trials and subsequent correspondence from Raphaela Jarvis, Assistant Executive Secretary, ADHREC,

Kindest regards,

Yours sincerely,

Bruce Short
Air Vice-Marshal
Chair ADHREC

EYE SURGEONS

22 WALTER STREET, NORTH ADELAIDE SA 5006

Dr John L Crompton
F.R.A.C.O.
Provider No. 0233144A
Special interests:
Neuro-Ophthalmology
Orbital Surgery
Ocular Motility

Dr Grant L Raymond
F.R.A.C.S., F.R.A.C.O.
Provider No. 0402515T
Special interests:
Vitreo-Retinal Surgery
Age-Related Macular Disease
Diabetic Eye Disease

Dr Garry J Davis
F.R.A.C.S., F.R.A.C.O.
Provider No. 0581264AH
Special interests:
Lid and Lacrimal Surgery
Orbital Surgery
Thyroid Eye Disease

[redacted]

29 August 2001

Raphaela Jarvis
Assistant Secretary
Australian Defence Human Resources Committee

Dear Madam,

RE: Tafenoquine and Mefloquine, and Drug-Induced Keratopathies
2000/7416/2 DHSB 1148/01

1. Vortex keratopathy refers to the whorl or vortex patterns seen in corneal epithelium (outer skin of the eye) in various conditions ranging from epithelial healing to hereditary enzyme deficiency of Fabry's disease and to systemic administration of various drugs. The strikingly similar morphological appearance caused by such a dissimilar array of underlying conditions suggests that a common mechanism is responsible for generating these patterns. Bron in 1973 first suggested that the vortex configurations probably are manifestation of the growth and repair process of the corneal epithelium (Bron A J; Vortex Patterns of the Corneal Epithelium, Trans Ophthalmol Soc, UK, 93:455, 1973). Epithelial cells arise from the limbal stem cells in the limbal area (junction of the white scleral of the eye and clear cornea) and move inwards at varying rates from the different parts of the corneal limbus to an area about one third of the distance upwards from the lowest part of the cornea. It is thought that this flow of cells from the periphery towards this special area (the "graveyard" of the corneal epithelium) is responsible for the whorl-like pattern commonly seen clinically.

s47f

The commonest drugs causing the drug-related vortex keratopathies are Chloroquine and Amiodarone but are also reported with Hydroxychloroquine, Quinacrine, Amodiaquine, Chlorpromazine, Pethidine and Indomethacin (Duane's Clinical Ophthalmology, Tasman W & Jaeger E A, Lippincott – Raven, Philadelphia, 1995, Volume 4, Chapter 17, page 6). The appearance of the slit-lamp microscope is that of grey-yellow-brown corneal epithelial deposits that are symmetric and bilateral. They appear in a vortex pattern from a horizontal line below the pupil and swirl outward generally sparing the limbus. It has also been noted that once these deposits reach the fully developed whorl configuration, the keratopathy does not progress but instead gradually disappears after the drug has discontinued. Electron microscopic studies have shown these epithelial deposits to be complex lipid within lysosomal intracytoplasmic inclusions. They represent the ability of cationic amphiphilic drugs to induce a generalized intralysosomal accumulation of polar lipids (Lullmann H, Rauch R, Wassermann O: Lipidosis Induced by Amphiphilic Cationic Drugs, Biochem Pharmacol 27:1103, 1978). Another morphologically similar corneal whorl pattern is seen in heavy pigmented patients wherein limbal pigment extends into the corneal epithelium due to epithelial pigment slide.

2. Having studied the documents provided from ADFREC on Tafanoquine, I do not believe that Tafanoquine will cause any permanent visual problems. I have seen many hundreds of patients with drug-induced vortex keratopathy and the vast majority have no visual disturbance whatsoever, and only one or two have had their best corrected visual acuity reduced by half to one line on the Snellen chart (the visual letter charts used for measuring visual acuities). Likewise, it is my opinion that I would predict that Tafanoquine will not have any long-term ophthalmic sequelae like

all the other drug-induced keratopathies, the drug deposition will fade completely with time.

As regards the trial itself, it would seem that there is an apparent weakness in the design of the trial resulting from the subsequent finding of some retinal (fundal) abnormalities in the follow-up period. This has created the current confusion as to whether or not these lesions are new or whether the pre-trial examination was insufficiently rigorous . I would recommend that for future similar trials, that fundus photographs taken prior to the trial provide the best (but expensive) baseline. Such documentation would certainly have prevented any such confusion and allowed scientific assessment as to whether or not the drug was associated with any pathological developments in the retina. From what I have read in the documents, I would very much doubt as to whether Tefanoquine has caused any of the findings reported in the retina, ie that the retinal changes were either there all along or whether they are simply age related developments and not associated with the administration of the drug. Clearly those soldiers found with fundus abnormalities will need long-term follow-up to determine stability.

3 Of course, any side-effects need to be considered against any proven increase in the efficacy as to the drug's anti-malarial action.

J L CROMPTON
Colonel
Consultant in Ophthalmology to the
Surgeon General, Australian Defence Force
jlc/bz/me

the remaining 1/3 are resolving. This requirement was almost achieved at the 10-week post last dose (61% complete resolution).

- Other eye examinations (except three retinal angiograms) have been normal.
- Of the 17 personnel who had retinal angiograms, three were abnormal. Two of these three were classed as variants of normal. The third was blatantly abnormal, reflecting an abnormal retina. The abnormalities observed are typical of environmental effects and it is believed that the abnormality is unlikely to be drug related. There are a number of other environmental factors that have been linked with causing the effects seen in the on abnormal case. The FDA has accepted this assessment.

4. From investigation of the SAE, the side effect profile of Tafenoquine related to corneal changes can be described as:

- Uniform
- Cumulative dose
- Asymptomatic
- 10 week resolution

5. The way ahead: Lieutenant Colonel Nasveld reported that 1,600 ADF personnel have been exposed to Tafenoquine through AMI trials. 1000 of these volunteers were involved in a three dosing day trial. Lieutenant Colonel Nasveld as the Principal Investigator of this trial would like to contact these volunteers and inform them of the findings of the changes in the cornea. As the corneal change is believed to be dose dependent, it is unlikely that these 1000 volunteers would have had any corneal changes. None the less, Lieutenant Colonel Nasveld would like to further investigate the effect of the corneal changes after a short course of Tafenoquine, such as that undertaken by the first 1000 ADF personnel involved in AMI research trials. This research would be an extension to the initial trial, using GMP product and providing additional data on the appearance of corneal changes as a result from exposure to Tafenoquine.

6. In the long term, AMI would like to undertake a three-month Tafenoquine trial for the prevention of vivax Malaria relapse. This trial would give a dose equivalent to 60% of that achieved in the six-month trial (216/00). Information gathered from this trial would provide further investigation of the SAE; corneal changes would be monitored, providing information relating to time to onset.

7. Undertaking the three day trial (272/01) would consolidate the study picture, enabling AMI to provide all volunteers and their RMO's with comprehensive information regarding the SAE's and the ensuing investigations, enabling full dissemination of information, minimising anxiety of the volunteers.

8. Lieutenant Colonel Nasveld then briefed the committee on some of the specifics of the two proposed trials.

(2) Protocol 267/01 – Evaluation of Tafenoquine™ for the Prevention of Vivax Malaria Relapse

9. Lieutenant Colonel Nasveld informed the committee that in a sample of 27 patients treated with Chloroquine and Primaquine, there were nine relapses within a 12-month window, using Tafenoquine for eight weeks, from 28 patients there was only one relapse. Tafenoquine is more effective at preventing relapse malaria then Chloroquine/Primaquine. This protocol has a three-month treatment ensuring there is enough time to establish a sufficient loading dose.

10. This study will also provide information regarding time of onset of the corneal changes.

(3) Protocol 272/01 – Evaluation of Tafenoquine for the Post Exposure Prophylaxis of Vivax Malaria (Southwest Pacific Type) in Non Immune Australian Soldiers – Ophthalmology Tolerability.

11. This protocol has being designed to establish further information regarding the use of GMP product and the ophthalmological effects of Tafenoquine that will complement the earlier trial of a three-day dosing of Tafenoquine. The approval of this protocol will be acknowledged by the FDA as an indication to reactivate the IND approval.

12. The Chair then asked Lieutenant Colonel Peter Nasveld and Lieutenant Commander Sonya Bennett to be excused. Lengthy discussion took place regarding the proposed studies. The usefulness and length of AMI presentations to the committee was commented on. Discussions included comment on the need to ensure a nominal role of participants in these studies, the moral and ethical obligations to investigate further the causal relationship to the potentially 1/17 finding of abnormal retinas after dosing with Tafenoquine. There is an obligation between the researcher and the volunteers that is separate to the obligations between the researcher and the supply company, GSK, to ensure further research and investigation of any adverse findings is undertaken. The committee found a number of deficiencies in the consent/information sheet that need to be addressed. The committee requires that the researchers report to the committee after the completion of the data collection from protocol 272/01, rather then the usual six-month reporting period.

Recommendation:
The meeting resolved to approve the use of Tafenoquine, and the two above protocols with the following provisions:

(1) Protocol 267/01 – Evaluation of Tafenoquine™ for the Prevention of Vivax Malaria Relapse

a. The consent form is amended to include in the Risks/Discomforts section a statement to the effect "Tafenoquine has been found to be related to reversible changes in the front of the eye. Long term studies of the drug are yet to be completed" and "it has not yet been registered with the regulatory authorities in Australia".

(2) Protocol 272/01 – Evaluation of Tafenoquine for the Post Exposure Prophylaxis of Vivax Malaria (Southwest Pacific Type) in Non Immune Australian Soldiers – Ophthalmology Tolerability.

a. The AMI report to ADHREC at the completion of the data collection, not the usual six month reporting time frame.

For Action:
Exec Sec
Assistant Exec Sec

13. The Chair then thanked Lieutenant Colonel Nasveld and Lieutenant Commander Bennett for their attendance, and they left the meeting.

26 November 2001

e. Protocol Audit Reports

(1) Protocol 216/00 – A Randomized, Double-Blind, Comparative Study to Evaluate the Safety, Tolerability and Effectiveness of Tafenoquine and Mefloquine for the Prophylaxis of Malaria in Non-Immune Australian Soldiers Deployed to East Timor.

19. Major Landy and Miss Jarvis visited the Army Malaria Institute in Brisbane to conduct an audit on the above protocol. At the time of the ADHREC audit, there were two other audits being conducted, one by Glaxo SmithKline, and the other by the US Army Medical Materiel Development Activity. Major Landy informed the committee that the ADHREC audit team was very well received by the unit, and that the level of record keeping was of a high standard.

20. During the course of the audit, it was found that there was one consent form missing. The unit has undertaken to inform ADHREC when this form is located.

21. Doctor Twomey asked if there was a process of random auditing available to ADHREC, and whether it was outlined in the guidelines for researchers. Major Landy explained that random auditing would be constrained by the ADHREC budget, and that there was no requirement as such for HRECs to conduct audits on trials. There was uncertainty as to whether random auditing was mentioned in the guidelines for researchers

Recommendation:
Provide advice to ADHREC on whether there is mention of random audits in the guidelines for researchers.

For action:
Exec Sec
Assistant Exec Sec

25 February 2002

e. Protocol 216/00 – A Randomized, Double-Blind, Comparative Study to Evaluate the Safety, Tolerability and Effectiveness of Tafenoquine and Mefloquine for the Prophylaxis of Malaria in Non-Immune Australian Soldiers Deployed to East Timor.

(1) Safety Update.

13. It was the feeling among the Committee that, whilst the information provided in this safety report was reassuring, it would be preferable to have all information conveyed openly and honestly to every member involved in current and previous Tafenoquine trials. This will markedly reduce the risk of a perceived cover up.

Decision

The Principal Investigator is to provide a copy to ADHREC for review of the draft

letter from Glaxo SmithKline that is proposed to be distributed to subjects.

For Action:
Exec Sec

c. Introduce Lieutenant Colonel Peter Nasveld and Lieutenant Commander Sonya Bennett, Protocols 216/00 – A Randomised, Double-Blind, Comparative Study to Evaluate the Safety, Tolerability and Effectiveness of Tafenoquine and Mefloquine for the Prophylaxis of Malaria in Non-Immune Australian Soldiers Deployed to East Timor and 292/02 – A Randomised, Double-Blind, Phase 2 Study of the Safety, Immunogenicity and Duration of Immunity of Chimerivax™-JE, Live Attenuated Vaccine in Healthy Adults.

3. The Chair invited Lieutenant Colonel Peter Nasveld and Lieutenant Commander Sonya Bennett to address ADHREC. Lieutenant Colonel Nasveld informed ADHREC that the research relating to Protocol 216/00 is now complete. The eye changes that were previously reported in some patients have now resolved, and there have been no further reports of visual disturbances experienced by any patient.

4. During the course of the analysis of the data collected, it was noted that there were a number of patients whose serum creatinine levels did not return to baseline, although they stayed within the normal range. Amendment 7 was written to address this issue. Lieutenant Colonel Nasveld asked ADHREC to consider whether it would be appropriate for the continued investigation of these patients to be conducted as clinical follow up instead of as a formal amendment to the Protocol. He stated that this would prevent further delay in the assessment of these patients. He also requested that ADHREC consider appointing a renal physician to assist in the assessment of any patients whose serum creatinine is found to be still above baseline at the follow up assessment. He said that this had been a recommendation from Glaxo SmithKline's renal consultative group.

5. Lieutenant Colonel Nasveld stated that, with ADHREC's approval, it was the intention of the researchers to close the study, but to continue to clinically monitor the patients who had been involved in the trial.

6. Lieutenant Colonel Nasveld and Lieutenant Commander Bennett were then asked to wait outside while the proposals were discussed.

DEFENCE
PERSONNEL

ADHREC
Australian Defence Human
Research Ethics Committee
[illegible]
Department of Defence
Canberra ACT 2600

PE 2600/156051
ADHREC 216/00
DHSB C[illegible]/2003

Lieutenant Colonel P.E. Nasveld
Research Officer
Australian Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

Dear Lieutenant Colonel Nasveld

AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE (ADHREC) PROTOCOL 216/00: A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR

1. ADHREC has considered your request with regards to the issuing of the letter *Dosing With The Study Drug Tafenoquine* to all study participants. This Distribution has been cleared by ADHREC to proceed.

2. The Committee wishes you well. Please contact me if I can be of any assistance.

Yours sincerely,

s22 [redacted]

KERRIE BRODERICK
Assistant Executive Secretary
Australian Defence Human Research Ethics Committee

21 February 2003

DEPARTMENT OF DEFENCE
AUSTRALIAN ARMY MALARIA INSTITUTE

Gallipoli Barracks, Enoggera, Queensland 4052

548-7-41

Insert Address Block

Dear Study Participant

DOSING WITH THE STUDY DRUG TAFENOQUINE

In *(insert year)* you were given the drug TAFENOQUINE for *(insert duration x days/weeks/months)*, under my care, as part of a malaria study to assess the safety and effectiveness of this drug that is under development by the drug company GlaxoSmithKline and the US Army. This study was run by the clinic at (*insert location*).

Nearly 3000 people, including yourself, have been given TAFENOQUINE in studies. These people have been recruited from Australia, Asia, Africa, Europe and the United States. No serious problems, or long term effects, have been reported with TAFENOQUINE since dosing began in humans over 5 years ago.

In a recently completed study in soldiers given TAFENOQUINE for 6 months, a group of the soldiers had additional examinations of their eyes – both before the study began, and at the end of the study after taking the drug for 6 months. In this group many of the soldiers who received TAFENOQUINE developed tiny deposits on the front of their eyes (the cornea). It is important for you to know that none of these soldiers had any symptoms – their vision was not affected in any way. Exactly the same changes are seen with other drugs used all over the world for a variety of diseases and conditions. This includes the drug chloroquine that has been used for many years in treating and preventing malaria. With all these drugs it is also important for you to know that these deposits disappear completely, given time. We know from the examinations in the soldiers that, for TAFENOQUINE, deposits disappear after about 6 months. You may have received TAFENOQUINE for a far shorter time period than these soldiers. We do not believe these deposits have any long-term effects on your eye or your vision.

Very recently a group of expert eye doctors from all over the world met in America to review the findings in the soldiers and provide advice. They agreed that these deposits were of little concern, would completely disappear with time, they do not affect vision, and are not a reason to stop taking drug. This group of doctors also reviewed other examinations on these soldiers – such as how well they could read letters on a chart, colour vision, and looking at the back of the eye. They confirmed that none of the soldiers had suffered any loss of vision as a result of taking TAFENOQUINE.

We hope you find this information reassuring, in that there is currently no evidence that vision has been affected in any subject given TAFENOQUINE. If you finished your study more than 1 year ago, these totally harmless deposits are extremely unlikely to be present.

However, if you are still concerned, you may want to contact your local doctor or clinic for further advice. Please, make an appointment by contacting your local Regimental Aid Post or Medical Centre for initial assessment. If your doctor thinks that further specialist assessment is required, he/she will then contact us at the Malaria Institute to arrange suitable followup.

You should take a copy of this letter with you to your appointment so that your doctor can advise us of any findings or followup required. Additionally, we would appreciate it if you could sign and date the copy of the letter included and return it to us in the pre-paid envelop provided so that we can be sure that this information has reached you. Alternatively, you may wish to acknowledge receipt or seek clarification by emailing the Principal Investigator at the email address listed below.

Yours sincerely

PETER NASVELD
Lieutenant Colonel
Principal Investigator

Double click here to add promulgation date

I, _____, acknowledge receipt of the above information.

(please print name clearly)

Signature of Study Volunteer:_____

Vol ID number*(if known)*:_____

Date:_____

FOLIO
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DEFENCE
PERSONNEL

ADHREC
Australian Defence Human
Research Ethics Committee
CP2-7-066
Department of Defence
Canberra ACT 2600

2000/15605/1
ADHREC 216/00
DHSB 2772 /2002

Lieutenant Colonel P.E. Nasveld
Research Officer
Australian Army Malaria Institute
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

Dear Lieutenant Colonel Nasveld

AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE (ADHREC) PROTOCOL 216/00: A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR

1. Thankyou for submitting for protocol safety update dated 23 January 2002. The update was reviewed by the Australian Defence Human Research Ethics Committee (ADHREC) on Monday the 25th February 2002.

2. ADHREC has considered the update and it was the feeling among the Committee that, whilst the information provided in this safety report was reassuring, it would be preferable to have all information conveyed openly and honestly to every member involved in current and previous Tafenoquine trials. This will markedly reduce the risk of a perceived cover up. As such, ADHREC still requires you, as the Principal investigator in the current and previous Tafenoquine trials, to inform all previously dosed Tafenoquine subjects of the ophthalmological findings. ADHREC requires a copy, for review, of the draft letter from Glaxo SmithKline, to be distributed to subjects.

3. Thank you again for your cooperation in the conduct of this trial. Please contact me if I can be of any assistance.

Yours sincerely,

s22 [redacted]

R.A. LANDY
Major
Executive Secretary
Australian Defence Human Research Ethics Committee

13 March 2002

Decision:
It was felt among the members that the researchers were displaying due diligence in following up on results that, even though they were still in the normal range, were not back to pre-trial levels. It was decided that;

(1) it would be appropriate for the affected patients to be clinically monitored, rather than amend the protocol,

(2) amendment 7 to Protocol 216/00 would be withdrawn, and

(3) a renal physician would be appointed to assist with clinical follow up if required.

For action:
Exec Sec
Assistant Exec Sec

f. Protocol 216/00: Randomised, double blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor- Antibody studies

Researchers requested that samples be re-tested using new technology and equipment. The samples are being tested for Malaria, as per the original consent/information process. The committee noted and ratified the decision.

Decision: ADHREC concurred that the samples can be tested using the new technology. It requested researchers submit a formal request for extension of the protocol.

Action by:
Exec Sec
Assist Exec Sec

d. Protocol 216/00: A randomized, double-blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor – Antibody studies.

70. ADHREC noted that the extension letter and approval out-of-session

Decision: No further action required.

7. Exec Sec was questioned at length as to why the progress report for **Protocol 216/00 A Randomized, Double-Blind, Comparative Study To Evaluate The Safety, Tolerability And Effectiveness Of Tafenoquine And Mefloquine For The**

Prophylaxis Of Malaria In Non-Immune Australian Soldiers Deployed To East Timor is still overdue. She stated on a number of occasions that, by her recollection, Army Malaria Institute (AMI) were still waiting for further reports from the overseas sponsors of the study. Despite stating that she would confirm this with AMI, the issue was raised again later in the meeting, but Exec Sec was unable to add anything to her previous response. ***Note by Exec Sec: For brevity, the issue is dealt with in full here. The protocol was initially closed on 12 June 2002, but re-opened following a request to do so by AMI on13 July 2005. ADHREC granted an extension on 1 August 2005 until 31 December 2007, to enable further analysis of samples which have been sent to America. As was recalled by Exec Sec, the final report from GlaxoSmithKline is still being awaited. Exec Sec spoke to Commanding Officer Army Malaria Institute on 4 July 2006. Lieutenant Colonel Cooper will provide a progress report to Exec Sec as a matter of urgency. A package summarising key events to do with Protocol 216/00 is enclosed with these Minutes***

(2) ITEM EIGHT – FINAL REPORTS

Protocol 216/00: A randomised, double-blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor.

Discussion occurred as to the apparent efficacy of both agents, with a different side-effect profile being the main differences.

Decision: Letter of thanks to be sent to the researcher.

Action:
Exec Sec
Asst Exec Sec

ITEM EIGHT – FINAL REPORTS

Protocol 216/00: A randomized, double – blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers deployed to East Timor. Support Paper.

30. Letter of thanks to the Researchers.

Decision: Letter of thanks to the Researchers.

Action:
Exec Sec
Asst Exec Sec

Australian Government
Department of Defence
Defence Personnel Executive

DEFENCE HEALTH SERVICES
CP2-2-121
Campbell Park
CANBERRA ACT 2600

PE 2000/15/05/1
ADHREC 216/00
DHSE [illegible] 2005

Modification approval

Lieutenant Colonel Peter Nasveld
Principal Research Clinician, AMI
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

Dear LTCOL Nasveld

AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE (ADHREC) PROTOCOL 216/00: A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR – ANTIBODY STUDIES

1. Your submission to use stored specimens to undertake antibody studies to determine malaria exposure was considered by the ADHREC at the meeting of 4th July 2005. The Committee considered that the request was consistent with the initial protocol and informed consent form and represented an alternative method of evaluating exposure to malaria, which was not sufficiently developed to be specified in the initial protocol. The Committee agreed that the consent provided by subjects at recruitment for the study is sufficient to meet the requirements for use of the specimens stored at AMI for the proposed purpose. The use of the samples is specifically restricted to tests for malaria exposure.

2. This information was communicated by email along with the requirement to formally request an extension of the study window beyond the originally approved 3 years. We note that you have formally requested this extension till 31st December 2007, and this extension has been approved as of 25th July 2005

3. ADHREC requires you to provide six-monthly progress reports, the next being due on 25 January 2005. ADHREC's compliance with the NHMRC *National Statement on Ethical Conduct in Research Involving Humans* requires that your progress reports include any events of significance occurring in the conduct of the protocol, and, where applicable, comment on: the security of your records; compliance with the approved consent procedures and documentation, and compliance with any other special conditions that ADHREC may have required.

4. If your protocol requires any modification, ADHREC approval must be sought in writing, detailing all modifications required.

5. The Committee wishes you well with your research. Please contact me if I can be of any assistance.

Yours sincerely

s22 [redacted]

DR R.A LANDY
Executive Secretary
Australian Defence Human Research Ethics Committee

01 August 2005

DEPARTMENT OF DEFENCE
AUSTRALIAN ARMY MALARIA INSTITUTE

Gallipoli Barracks, Enoggera, Queensland 4052

548-7-41
ADHREC 216/00
AMI 65/05

Lieutenant Colonel Rosemary Landy
Executive Secretary
Australian Defence Human Research Ethics Committee
CP2-7-6
Campbell Park, ACT, 2600

Dear

EXTENSION OF APPROVALS FOR ADHREC PROTOCOL 216/00 - A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR – ANTIBODY STUDIES

1. Following our discussions in Hanoi and further clarifying discussions with s47F of WRAIR, we would like to formally request ADHREC clearance to conduct follow on antibody screening on blood samples collected as a component of the subject trial. As discussed we believe the consent process undertaken during the subject trial is sufficient from the subject perspective to allow the use of existing samples for this purpose. Specifically that the subjects were aware in the consent process that the study was assessing the "Effectiveness" of the antimalarial agents in protecting them from malaria, and more directly under Study Tests in the Consent Form they gave permission for "checking your blood for malaria".

2. The attached US Army Protocol identifies tests of exposure to malaria, which were not available at the time of the initial study conduct. They represent a significant step forward in determining whether or not subjects may have been exposed to malaria infection, but because of adequate prophylaxis failed to manifest as clinical disease. In other words, whether the drugs used were effective in preventing malaria. The introduction to this protocol outlines the advantages of following this path in the current climate of restrictions to placebo controlled trials which may otherwise have given these answers.

3. As the final study report has not been registered with ADHREC, AMI have retained all existing samples for this study in keeping with our extant policy of retaining all study materials until all study activity has been finalised. AMI have been aware of the possibility of using these samples to define exposure as more promising technologies became available and in fact have continued to be in the discussion loop for the concept of surrogate markers of exposure since the formation of the original study design. The intent has always been to test these samples for exposure if and when technological advances made such an assessment possible.

4. If testing succeeds in identifying sufficient exposure of our subjects without patent disease, it is possible that the subject trial would be rated as "pivotal" in the development of this compound and result in significant logistic savings in moving Tafenoquine towards market availability.

5. Given that subjects have ceased their direct study involvement upto 4 years ago, it is considered impractical to reinitiate the consent process. Recent experiences already reported to ADHREC regarding followup communication with these subjects regarding unexpected eye findings during the study, saw 166 of the 654 subjects return acknowledgments (prepaid return to AMI) indicating that they had received the information. This is a relatively poor return given the considerable effort that

went into the notification process. A requirement to re-consent specifically for this activity would be unlikely to achieve a better outcome and would result in the ADF sample set not being available in the time frame required for their inclusion in this promising sub study.

6. We have considered the potential impact of the activity on the subjects. We believe there is no detriment to the subjects as all samples are de-identified except by study number and date of collection. We retain at AMI the only listing that could link the subject number to a specific subject, and under existing arrangements are fully aware of our responsibilities for maintaining this confidentiality. Additionally, the findings of malaria exposure in a subject would not require any further specific followup with that subject as any clinical episode of malaria since that time would have been manifest well before now.

7. We also acknowledge that there is no direct benefit derived by the subject in the use of their samples in this study, but believe the benevolence considerations of a potential development of robust surrogate markers for this disease meets the ethics test or no malevolence and a community benevolence.

8. AMI request consideration of this proposal as a way of progressing our knowledge of exposure risk in deployed ADF personnel and of contributing to the overall development of alternative study designs and strategies that will allow the development of promising antimalarial candidate drugs in a revised Helsinki Declaration environment that imposes constraints on placebo controlled trial activity. Success with this project stands to revolutionise the approach to the conduct of malaria clinical studies in the future.

9. On your approval we would request WRAIR to modify the attached protocol by amendment to reflect the inclusion of AMI samples and to include AMI in the listings of collaborating Institutions and personnel. This will ensure that the ADF obtains some oversight and benefit from association with the project.

10. Funding is available to undertake this project in the current US Fiscal Year04, so your prompt consideration would be appreciated.

Yours sincerely

PETER NASVELD
Lieutenant Colonel
Principal Researcb Clinician

23 May 2005

Attachements:

1. Information and Consent Form ADHREC 216/00

2. US Army Protocol

Australian Government
Department of Defence
Defence Personnel Executive

DEFENCE HEALTH SERVICES
CP2-2-121
Campbell Park
CANBERRA ACT 2600

PE 2000/15605/1
ADHREC 216/00
DHSB /2005

Lieutenant Colonel Peter Nasveld
Principal Research Clinician, AMI
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

Dear LTCOL Nasveld

AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE (ADHREC) PROTOCOL 216/00: A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR – ANTIBODY STUDIES

1. Thankyou for providing a request for extension letter. The extension to continue the study until 31 December 2007 has been approved.

2. ADHREC requires you to provide six-monthly progress reports, the next being due on 25 July 2005. ADHREC's compliance with the NHMRC *National Statement on Ethical Conduct in Research Involving Humans* requires that your progress reports include any events of significance occurring in the conduct of the protocol, and, where applicable, comment on: the security of your records; compliance with the approved consent procedures and documentation, and compliance with any other special conditions that ADHREC may have required.

3. If your protocol requires any modification, ADHREC approval must be sought in writing, detailing all modifications required..

4. The Committee wishes you well with your research. Please contact me if I can be of any assistance.

Yours sincerely,

DR R.A LANDY
Executive Secretary
Australian Defence Human Research Ethics Committee

28 July 2005

DEPARTMENT OF DEFENCE
AUSTRALIAN ARMY MALARIA INSTITUTE
Gallipoli Barracks, Enoggera, Queensland 4052

54

548-7-41
ADHREC 216/00
AMI 92/05

Lieutenant Colonel Rosemary Landy
Executive Secretary
Australian Defence Human Research Ethics Committee
CP2-7-6
Campbell Park, ACT, 2600

Dear Rosemary

EXTENSION OF APPROVALS FOR ADHREC PROTOCOL 216/00 - A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR – ANTIBODY STUDIES

1. Thankyou for your timely response by email to our previous request to extend the scope of analysis on this study. You indicated that ADHREC had considered the submission and agreed in principle, but that a formal request to extend the period of the study to greater than 3 years would be required.

2. Please accept this correspondence as the formal request to extend the period of the study till 31st December 2007, which should be more than sufficient time to fine tune analysis techniques and conduct malaria exposure assessment.

3. Again, I would like to express my gratitude to yourself and the Committee for their continuing interest in this vital research.

Yours sincerely

(Original signed and sent)

PETER NASVELD
Lieutenant Colonel
Principal Research Clinician

13 July 2005

DEPARTMENT OF DEFENCE
AUSTRALIAN ARMY MALARIA INSTITUTE

Gallipoli Barracks, Enoggera, Queensland 4052

548-7-41
ADHREC 216/00
AMI 168/06

Lieutenant Colonel Rosemary Landy
Executive Secretary
Australian Defence Human Research Ethics Committee
CP2-7-6
Campbell Park, ACT, 2600

Dear Rosemary

CLARIFICATION AND STATUS REPORT FOR EXTENSION OF APPROVALS FOR ADHREC PROTOCOL 216/00 - A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR – ANTIBODY STUDIES

1. Following our discussions today we have reviewed the situation with the subject trial. As you will be aware the original study was closed out by ADHREC and notified to us as being closed on 12th June 2002 (PE2000/15605/1).

2. Following approaches from the US Army, including our conversations in Hanoi in May 2005, we requested from ADHREC permission to use the stored samples from this study to look at malaria antibodies, using newer techniques than were available at the time of the original study (548-7-41 AMI 65/05 dated 23rd May 2005). A new protocol specific to the proposed extension was forwarded to ADHREC at this time. The original response to us came from Tess Winslade by email indicating that the approval had been given but that the Committee had requested that we formally request an extension for the original study. Consequently, a second letter was sent on 13th July 2005 (548-7-41 AMI 92/05) formally requesting an extension.

3. A formal written response from ADHREC confirming the extension was sent on 1st August 2005, stating an ADHREC clearance date of 25th July 2005 and extending the project until 31st December 2007 (PE 2000/15605/1 ADHREC 216/00).

4. Following the receipt of this permission AMI undertook the specimen preparation required by the protocol. Subsequent to this activity the US Army withdrew funding for the project and no further analysis has been undertaken. Enquiries indicate that the required funding for this project is now unlikely.

5. It is noted that a report for this activity was due at 25th January 2006, and the Principal Investigator acknowledges that this report was not prepared in the required time frame, largely because there had been no study related activity.

6. AMI request that ADHREC:

a. Withdraw the Extension to Protocol 216/00

b. Maintain the Close-out of Protocol 216/00 as at 12th June 2002.

7. In the event that any new activity becomes possible, AMI will re-initiate communications with the Committee.

8. Thankyou for your assistance with this project and we remain disappointed that the extension did not go ahead considering the effort that had been put into place to get this interesting extension underway. Please pass on my appreciation to the Committee for the effort expended on this project, along with my apologies for any confusion that the extension process may have caused.

Yours sincerely

s22 [redacted]

PETER NASVELD
Lieutenant Colonel
Principal Research Clinician

4th July 2006

FOLIO

Australian Government
Department of Defence
Defence Support Group

Defence Health Services
CP2-7-121
Campbell Park
CANBERRA ACT 2600

2000/15605/3
ADHREC 216/00
DCO/OUT/2006/216

Lieutenant Colonel Peter Nasveld
Principal Research Clinician, AMI
Weary Dunlop Drive
Gallipoli Barracks
ENOGGERA QLD 4052

Dear LTCOL Nasveld

AUSTRALIAN DEFENCE HUMAN RESEARCH ETHICS COMMITTEE (ADHREC) PROTOCOL 216/00: A RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF TAFENOQUINE AND MEFLOQUINE FOR THE PROPHYLAXIS OF MALARIA IN NON-IMMUNE AUSTRALIAN SOLDIERS DEPLOYED TO EAST TIMOR – ANTIBODY STUDIES

1. Thank you for informing the Committee that this project has been completed and for providing a copy of your Final Report. Your report was presented at the ADHREC meeting on Monday 28th August 2006.

2. The Committee congratulates you on the completion of your project and wishes you all the best for any research ventures you may undertake in the future.

3. Our file has now been finalised.

Yours sincerely

s22 [redacted]

Doctor Rosemary A. Landy
Executive Secretary
Australian Defence Human Research Ethics Committee
CP2-7-068
Campbell Park Offices
CANBERRA ACT 2600

/ September 2006