To

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

From

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Dear Ms Beverly

Thank you for your invitation to make a written submission to the Committee on ADF use of Mefloquine and Tafenoquine. Please find below brief overviews of Medicines for Malaria Venture and *P. vivax* malaria – the disease that tafenoquine was developed to treat. This is followed by our comments regarding international evidence on the impact of Quinoline antimalarials and how other governments have responded to claims regarding Quinoline antimalarials. We also attach three appendices: *Appendix 1*- The US FDA's approved label for tafenoquine; *Appendix 2* - FDA briefing document on tafenoquine; *Appendix 3* – Incidence of Adverse Events.

Overview of Medicines for Malaria Venture

Medicines for Malaria Venture (MMV), the organisation I lead as CEO, is a leading product development partnership (PDP) in the field of antimalarial drug research and development. Our mission is to reduce the burden of malaria in disease-endemic countries by discovering, developing and facilitating delivery of new, effective and affordable antimalarial drugs. Our vision is a world in which these innovative medicines will cure and protect the vulnerable and under-served populations at risk of malaria, and help to ultimately eradicate this terrible disease.

In 1999, MMV was established to fill the virtually empty pipeline for new malaria drugs caused by falling interest from the pharmaceutical industry to pursue research and development (R&D) for neglected diseases. Today, we have a robust pipeline of 65 new drug projects spanning every phase of research and development from discovery of new compounds to clinical trials of promising antimalarial drugs.

In 2009, together with our partner Novartis, we launched our first co-developed drug, a high quality, child-friendly artemisinin combination. Since then, MMV and its partners, such as Guilin Pharmaceutical, Alfasigma-Pierre Fabre, Shin Poong Pharmaceutical, Sanofi, Cipla and Strides, have brought forward seven more new anti-malarial therapies that have saved over 1.5 million lives.

MMV's success in research and development, as well as access and product management, comes from its extensive partnership network of over 160 active pharmaceutical, academic and endemic-country partners in more than 50 countries. MMV works closely with the World Health Organization, and is funded by donors including the governments of Australia, Ireland, Japan (the GHIT fund), the Netherlands, Norway, Switzerland, the UK and the USA; the Bill and Melinda Gates Foundation and the Wellcome Trust.

***Plasmodium vivax (P. vivax)* malaria**

P. vivax malaria is responsible globally for a very significant burden of illness. In its 2017 World Malaria Report, the World Health Organization (WHO) estimated that there were around 8.5 million clinical cases of *P. vivax* malaria in the previous year, of which 5.3 million were in the Asia-Pacific region.

The *P. vivax* infection consists of both blood and liver stages. The blood-stage infection is treated with quinine, chloroquine or artemisinin combination therapies (ACTs), but this does not rid the body of all forms of the parasite. One form, the hypnozoite, can lie dormant in the liver in a form that can periodically

reactivate, leading to a relapse of malaria which contributes to the burden of disease in the individual patient, and also to the onward transmission of the infection. *P. vivax* malaria patients, who do not receive treatment for the relapse, experience repeated episodes of chills, vomiting, malaise, headache, fever and myalgia. *P. vivax* has also been shown to cause severe anaemia, respiratory distress, malnutrition, coma and, in severe cases, death.

Currently, primaquine (PQ) is the gold-standard treatment for the radical cure of *P. vivax* malaria. However, the drug needs to be administered daily, over a period of 2 weeks. Patient compliance with the full 14-day treatment course of PQ is reported as being as low as 30% and that poor compliance, as seen with unsupervised or semi-supervised administration, can lead to a 3-fold to 4-fold reduction in efficacy (Abreha et al 2017[1]; Khantiku, 2009[2]). Thus, a clear need exists for a simpler alternative treatment for relapsing malaria that can facilitate improved compliance.

Short history of tafenoquine

To meet this need, MMV and GSK have been investigating the use of TQ, a compound from the 8-aminoquinoline class of drugs, as a potential anti-relapse treatment administered in just one 300mg single dose to patients infected with relapsing, *P. vivax* malaria.

The phase IIb/III development program undertaken by GSK and MMV demonstrated substantial efficacy for tafenoquine (TQ), with an appropriate safety profile throughout the 6-month follow-up. Furthermore, the risks of haemolysis in G6PD deficient patients could be safely managed by testing prior to treatment. (This risk is of concern because TQ, like PQ, carries a risk of haemolysis in patients deficient in the enzyme G6PD.). A rapid point-of-care diagnostic for G6PD enzyme activity is in development in parallel with the tafenoquine development program.

Safety and efficacy of tafenoquine

A new drug application (NDA) for tafenoquine was submitted by GSK to the FDA in November 2017 and a regulatory submission was also made to the Australian Therapeutics Good Administration (TGA) in December 2017.

On 12 July 2018, a 13-member panel of the Antimicrobial Drugs Advisory Committee (AMDAC) of the United States Food and Drug Administration (FDA) convened to provide the FDA with independent expert advice on the safety and efficacy of tafenoquine. AMDAC provides non-binding recommendations for consideration by the FDA.

After the hearing, at which multi-disciplinary experts provided individual testimonies, the 13-member Committee voted in favour of the safety and efficacy of tafenoquine. It stated that substantial evidence ~~existed of the effectiveness (13 f~~or; 0 against) and adequate evidence of the safety (12 for; 1 against) of

[1] Abreha A *et al.* Comparison of artemether-lumefantrine and chloroquine with and without primaquine for the treatment of *Plasmodium vivax* infection in Ethiopia: A randomized controlled trial. *PLoS Med* 2017;14:e1002299.
[2] Khantikul N *et al*. Adherence to antimalarial drug therapy among vivax malaria patients in northern Thailand. *J Health Popul Nutr* 2009;27:4–13.

single-dose tafenoquine for the radical cure (prevention of relapse) of *P. vivax* malaria in patients ≥16 years of age.

This announcement was followed a week later by the US FDA's approval of single-dose 300mg tafenoquine (US proprietary name: KRINTAFEL) for the radical cure of *P. vivax* malaria.

The approval was based on efficacy and safety data from a comprehensive global clinical development *P. vivax* radical cure program designed in agreement with the FDA. Thirteen studies in healthy volunteers and patients directly supported the program. The primary evidence for the clinical efficacy and safety of the 300mg single-dose, to which more than 800 subjects were exposed, was provided by three randomized, double-blind studies: DETECTIVE Part 1 and Part 2 (TAF112582) and GATHER (TAF116564). The results of the two phase III studies were announced in June 2017. The submission included data analyzed from a total of thirty-three studies involving more than 4,000 trial subjects exposed to any dose of tafenoquine.

Identified potential risks are described in the approved US label (*Appendix 1*) and enhanced pharmacovigilance measures are currently being developed by GSK in consultation with the WHO.

Adverse events

In relation to the subject of the Australian Senate Inquiry, it should be noted that no serious neurological or psychiatric adverse events (AEs) were noted in the clinical efficacy & safety studies that investigated the single 300mg tafenoquine treatment dose (GSK-MMV clinical trials program for TQ), and no subjects withdrew from the studies or discontinued treatment due to central nervous system (CNS) AEs. All CNS events seen in these studies were mild to moderate in severity and were self-limiting.

The incidence of CNS AEs over the full study period were similar in the TQ+chloroquine (TQ+CQ) and PQ+CQ treatment groups and lower than in the CQ alone group in these trials. This difference was driven primarily by AEs of headache, probably associated with malaria recurrence in this treatment group. *Appendix 3*.

Given this confounding factor, CNS events with onset during the first 29 days of the study (i.e., before any documented recurrence) were considered a more appropriate, albeit stringent, reflection of the AE profile for the active arms (TQ+CQ and PQ+CQ) compared to placebo (CQ only group).(Appendix 3) Using this more stringent analysis, the overall incidence of dizziness was higher for both TQ+CQ and PQ+CQ versus for CQ alone. This is consistent with the current labelling for primaquine. However, the overall incidences of other CNS events were similar across the treatment groups. In the TQ+CQ group, the events of anxiety and somnolence were Grade 1 or Grade 2 in severity and transient. These events were not considered to be related to study treatment by the investigators.

As outlined in the FDA Advisory Committee Briefing document, (*Appendix 2*) "*While there were no reports of serious psychiatric disorders following 300mg single dose TQ, cases of depression and psychosis have occurred in subjects following higher single doses of TQ (350mg to 600mg) or in multi-dose regimens (e.g., prophylaxis). Most of these events occurred in subjects with a previous history of*

psychiatric disorders." [3] In addition, *"Two cases of depression and 2 cases of psychosis were noted, following receipt of single-dose of TQ that were higher than the approved single 300mg treatment dose, and were seen primarily in patients with a prior history of psychiatric disorders"*.

We therefore conclude that in the >800 subjects who have received a total single-dose of 300mg TQ, no serious CNS events have been reported and the observed events have been mild to moderate and self-limiting. Therefore, the single 300 mg TQ dose + CQ for radical cure of *P. vivax* malaria is anticipated to have a low risk of significant CNS effects in patients without an active or past history of serious psychiatric disorders.

In support of this, non-clinical animal studies do not suggest a signal for CNS toxicity with tafenoquine. Neurobehavioral alterations and /or CNS-pathology with certain quinoline anti-malarials have been variously observed in mice, rats, dogs and/or rhesus monkeys.[4] Tafenoquine has been tested in such species (mice, rats and dogs) in single and repeat dose toxicology studies and did not induce neurotoxicity, or specific neurobehavioral changes, at exposures that are comparable to or in excess of those seen at the recommended treatment dose for patients. This conclusion is consistent with the conclusions provided by GSK and 60 Degree Pharma during their recent FDA Advisory Committee meetings. Furthermore, the US FDA concurred with these assessments. In his oral statement the FDA non-clinical toxicologist, Dr Owen McMaster, indicated that further testing in animal species would provide no additional value, as they "vary across species" and "would be difficult to interpret". His presentation concluded: *"The principal nonclinical toxicology findings were haematological, pulmonary, hepatic, renal and reproductive. Reversible or not adverse. TQ is not associated with neuro-behavioural or histopathology findings."*

Conclusion

Treatment with tafenoquine for the radical cure of *P. vivax* malaria, has been shown to be efficacious, with an acceptable safety profile in patients with ≥70% normal G6PD enzyme activity, with adverse events being generally mild to moderate and self-limiting in nature. We believe its use will transform case-management of *P. vivax* infection, improve compliance, help achieve improved rates of radical cure and contribute to achieving both the Sustainable Development Goals (SDGs) and malaria elimination targets set by WHO.

[3] FDA Advisory Committee Briefing Document (Section 6.5.4)
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm612873.htm

[4] FDA Advisory Committee Briefing Document (Section 3 – Toxicology; p.35)
[Dow 2006, Lee 1981, Korte 1979, Korte 1982, Schmidt 1948, Schmidt 1949, Schmidt 1950, Schmidt 1951]