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July 31, 2018

Lyn Beverly,
Committee Secretary,
Senate Foreign Affairs, Defence and Trade References Committee
PO Box 6100
Parliament House
Canberra, ACT 2600
Australia

RE ADF use of Mefloquine and Tafenoquine

Enclosures: Appendices 1-8.

Dear Ms. Beverly,

I am writing in response to your May 29th, 2018 request for submissions in relation to the Senate's inquiry into the use of antimalarials by the Australian Defence Force (ADF). I am the CEO and majority shareholder of 60 Degrees Pharmaceuticals LLC (60P), the global sponsor for tafenoquine for malaria prophylaxis. 60P has submitted a request for marketing approval to the U.S. FDA, and through an Australian sublicensee, to the TGA, in Australia. These dossiers are currently being reviewed, with decisions expected in the second half of 2018[1]. For your information, I have included my CV herein, which documents my professional scientific expertise in antimalarial drug development and the neurotoxicity of antimalarial drugs (**I request that my CV be reviewed in camera, and not publicly released**).

The "bottom line up front" of the testimony contained herein, is that scientific studies in animals and humans do not suggest that tafenoquine is neurotoxic. Furthermore, the suggestion by advocacy organizations that a causal relationship exists between tafenoquine administration and anecdotal reports of adverse events on social media 15+ years later is not supported by the facts. The U.S. FDA has concluded in regulatory briefing documents that tafenoquine is effective and reasonably safe.

In 1999, Prime Minister John Howard, with Cabinet, cross-bench, and public support, wrote President Habibie of Indonesia a letter suggesting that a referendum should be conducted regarding independence for Timor-Leste. This decision eventually resulted in deployment of a brigade-strength of Australian soldiers as peace-keepers under United Nations Security Council Resolution 1264. The Australian Defence Force (ADF), and the Australian Federal Police (AFP) and diplomatic personnel that followed, performed in exemplary fashion, providing the Australian government with a major foreign policy achievement without the loss of life from hostile fire.

[1] FDA approved GSK's application on July 20th, 2018. Other regulatory outcomes are pending.

However, in the early stages of that deployment, Australian soldiers experienced the highest incidence of malaria since the Vietnam War.[2] Five soldiers were evacuated to Royal Darwin hospital with severe malaria.[3] The spike in malaria morbidity occurred largely as a consequence of the failure of soldiers to comply with unobserved doxycycline prophylaxis.[4] As a consequence, a command decision was made to administer weekly antimalarials in most instances for the remainder of the campaign since the medical literature suggests there is a greater likelihood of compliance with weekly compared to daily drugs.[5] The wisdom of that decision is evidenced by the complete lack of malaria cases amongst ADF personnel in Timor later in the campaign.[6]

During the Timor-Leste, and subsequent Pacific deployments, the ADF conducted three clinical studies involving tafenoquine, the results of which have been published in peer reviewed medical journals.[7] GlaxoSmithKline, not 60P, was the industry co-sponsor of those studies at the time (60P was not incorporated until 2010). 60P, through contractual agreements with the United States Department of Defense, has secured the right to utilize data from those clinical studies in its global regulatory filings for malaria prophylaxis. Members of the advocacy community have alleged that these studies were unethical and involve coercion of Australian soldiers. These claims have been thoroughly discredited by an independent report from the Inspector General of the ADF (reference).[8] These studies have also recently been audited by the FDA in support of 60P's marketing application to FDA (with the TGA attending as an observer).[9]

Tafenoquine is an 8-aminoquinoline (8AQ) analog of Primaquine. Primaquine was first registered in the United States in 1952, and has been used for more than 60 years in the USA and Australia for treatment of *P. vivax* malaria and malaria prophylaxis in travelers for up to one year's duration.[10] Systematic reviews of the literature focus on the hematological and GI adverse events, not neurotoxicity, as the main adverse drug reactions of concerns with primaquine.[11] Product labeling in the United States for malaria prophylaxis does not involve specific warnings for psychiatric events.[12] Generally, after 60+ years of use, primaquine is not viewed by the scientific and medical community as causing an increased risk of psychiatric events.

Activist groups such as the Quinism Foundation, in common cause with some veterans' groups, (hereafter referred to as the "anti-tafenoquine activist community") bluntly assert that all quinoline antimalarials are neurotoxic.[13] This is false. Primaquine (referenced in the prior paragraph) is an 8-aminoquinoline. It is activated in the body to form unknown oxidative intermediates that confer an indirect antimalarial effect on hepatic stages without causing neurologic deficits (see prior paragraph). In contrast, mefloquine is a 4-aminoalcohol with a side chain and confers both a potent and direct effect only on blood stage malaria parasites, while inducing an increased rate of some specific neuropsychiatric events relative to the standard of care in travelers.[14] Since tafenoquine is an 8-aminoquinoline analog of primaquine, and is not structurally related to mefloquine, there is no reason, a priori, to expect it to exhibit the same adverse event profile as mefloquine.

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[2] Kitchener et al. *Med J Aust* **2000**; 173:583-585. Dow et al. *Mal J* **2014**; 13:49.
[3] Blum and Stephens. *Anaeth Intensive Care* **2001**; 29(4): 426-34.
[4] Dow et al. *Mal J* **2014**; 13:49
[5] Saunders et al. *Am J Trop Med Hyg* **2015**; 93:584-90.
[6] Nasveld et al. *Antimicrob Agents Chemo* **2010**; 54:792-780.
[7] Kitchener et al. *Am J Trop Med Hyg* **2007**; 76:494-496. Elmes et al. *Am J Trop Med Hyg* **2008**; 102:1095-1101. Nasveld et al. *Antimicrob Agents Chemo* **2010**; 54:792-780.
[8] See report from ADF Inspector General at: www.defence.gov.au/publications/coi/Docs/COI-AntiMalarialTrials.pdf
[9] This report is not available for public release.
[10] Fryauff et al. *Lancet* **1995**; 346:1190-1193. Baird et al. *CID* **2001;** 33**:**1990-1997. Recht et al **2014**. Safety of 8-aminoquinoline malaria medicines. World Health Organization, Geneva.
[11] Hill et al. *Am J Top Med Hyg* **2006**; **75**:402-15. Recht et al **2014**. Safety of 8-aminoquinoline malaria medicines. World Health Organization, Geneva.
[12] Hill et al. *Am J Top Med Hyg* **2006**; **75**:402-15.
[13] Press release from Quinism Foundation. Accessed July 28th, 2018 at: https://www.prweb.com/releases/2018/07/prweb15612420.htm
[14] Tickell Painter et al. *Cochrane Database Syst Rev* **2017**; 10:CD004791.

The anti-tafenoquine activist community notes that some 8-aminoquinolines were found to be neurotoxic in humans and monkeys in the 1940s and 1950s[15], and concludes that this means that all 8-AQs are neurotoxic. This is false. In fact, as we have stated in our advisory committee briefing document to the FDA, the literature shows that Schmidt's monkey toxicity studies correctly predict the lack of neurotoxicity at clinical doses, and wide therapeutic margin, of some 8-aminoquinolines, e.g. primaquine.[16] Furthermore, tafenoquine has structural features, e.g. a 4-methyl substitution, that are consistent with a lack of neurotoxicity[17]. Studies in rats, dogs and monkeys confirm the lack of neurotoxicity, and the FDA, in public statements at two advisory committee meetings, an FDA official noted that the toxicology package submitted was sufficient, that tafenoquine is not neurotoxic and additional animal studies are not needed.[18] This confirms prior conclusions of Australia's Repatriation Medical Authority that tafenoquine does not cause permanent brain injury.[19]

If regulatory agencies grant marketing approval for tafenoquine, the prophylactic dose will involve administration of a 200 mg x 3 load, followed by weekly 200 mg dosing during travel, followed by a single dose within one week of return. Peer reviewed clinical data suggest that in non-deployed individuals, the overall rate of adverse events was similar to placebo and the risk of adverse psychiatric events is not meaningfully increased.[20] Discontinuations due to psychiatric events thought by study investigators to be at least possibly related to tafenoquine were infrequent (0.3% incidence).[21] These all resolved. An elevated risk of psychiatric events in a deployed population relative to a non-deployed population was observed.[22] This is thought to be because deployment is a major risk factor for elevated incidence of neuropsychiatric events, and that the Timor operations were considered "warlike" by the Australian government.[23] We also note that there is a similar aggregate increase in the burden of neuropsychiatric events during deployment between mefloquine and atovaquone-proguanil, even though the latter drug is viewed by the anti-tafenoquine activist community to exhibit a benign neuropsychiatric safety profile.[24]

The TGA, through an FOI request, recently released summary details of 21 anecdotal reports of neuropsychiatric events.[25] These reports were submitted by, or on behalf of former veterans, who allege that they were caused by tafenoquine administration in the ADF clinical trials 15+ years earlier. The reports describe events that occurred during and/or many years after the studies. For seventeen of these cases for which 60P was able to obtain detailed case information from, it was possible to match line listings in the Sponsor's safety database to specific adverse event reports.[26] In our advisory committee briefing document for FDA, we report the results of our analysis of these cases, which was essentially that in all instances but one, contemporaneous accounts of adverse events could not

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[15] Schmidt & Schmidt. *J Neuropathol Exp Neurol* **1948**; 7:368-398. Schmidt & Schmidt. *J Comp Neurol* **1949**; 91:337-67. Schmidt & Schmidt. *J Neuropath Exp Neurol* **1951**; 10:231-256. Craige et al *J Clin Invest* **1947**; 27:17-24. Loken et al. *Am J Trop Med Hyg* **1949**; 29:341-52.

[16] Refer to the attached slide deck and to the briefing document 60P prepare for its FDA advisory committee meeting: 60 Degrees Pharmaceuticals LLC. 2018. Arakoda (Tafenoquine succinate) Tablets for Malaria Prevention in Adults: Briefing Document for FDA Antimicrobial Products Advisory Committee Meeting, July 26th, 2018. Accessible at: file:///C:/Users/geoff/Dropbox%20(60P)/60P%20Group%20Of%20Companies/Regulatory%20&%20Quality/UCM614202.pdf; Schmidt & Schmidt. *J Neuropath Exp Neurol* **1951**; 10:231-256; Schmidt et al. *Am J Trop Med Hyg* **1982**; 31 Supplement:666-680; Clayman et al. *J Am Med Assoc* **1952**; 149:1563-1568; Hill et al. *Am J Top Med Hyg* **2006**; **75**:402-15.

[17] Schmidt. *Antimicrob Agents Chemother* **1983**; 24:615-52.

[18] Dow et al. *TMID* **2017**; 17:28-34; 60 Degrees Pharmaceuticals LLC. 2018. Arakoda (Tafenoquine succinate) Tablets for Malaria Prevention in Adults: Briefing Document for FDA Antimicrobial Products Advisory Committee Meeting, July 26th, 2018. Accessible at: file:///C:/Users/geoff/Dropbox%20(60P)/60P%20Group%20Of%20Companies/Regulatory%20&%20Quality/UCM614202.pdf.; The statement made by the FDA was from Dr Owen McMaster, FDA toxicologist, at both the GSK and 60P advisory committee meetings on July 12th and July 26th. Meeting transcripts of the meetings had not yet been publicly released at the time of writing of this letter.

[19] Please refer to report from the Repatriation Medical Authority accessible at: http://www.rma.gov.au/assets/Other/RMA-Statement-of-reasons-chemically-acquired-brain-injury-29-August-2017.pdf.

[20] Novitt-Moreno et al. *TIMD* **2017**; 17:19-27.

[21] Novitt-Moreno et al. *TIMD* **2017**; 17:19-27.

[22] Novitt-Moreno et al. *TIMD* **2017**; 17:19-27.

[23] Waller et al. *BMC Psychiatry* **2012**; 12:1.

[24] Eick-Cost et al. *Am J Trop Med Hyg* **2017**; 96:159-166.

[25] Attached as an appendix to this letter.

[26] 60 Degrees Pharmaceuticals LLC. 2018. Arakoda (Tafenoquine succinate) Tablets for Malaria Prevention in Adults: Briefing Document for FDA Antimicrobial Products Advisory Committee Meeting, July 26th, 2018. Accessible at: file:///C:/Users/geoff/Dropbox%20(60P)/60P%20Group%20Of%20Companies/Regulatory%20&%20Quality/UCM614202.pdf

be verified as actually having occurred.[27] GSK reached broadly the same conclusion as did the FDA in an independent audit of ADF records.[28] Presumably the failure to verify anecdotal accounts of contemporaneous events is due to recall bias on the part of those making the reports. For events alleged to have occurred during or after 2007, it is not scientifically plausible that tafenoquine could have been a causative factor. Therefore, with the greatest respect to the veterans affected, their adverse experiences cannot, in 60P's view, be reasonably attributed to tafenoquine.

On July 12th, at the FDA's advisory committee reviewed data for GSK' tafenoquine-containing product, Krintafel™, for radical cure, and determined that the safety and efficacy of tafenoquine was adequate.[29] FDA granted regulatory approval for Krintafel™ on July 20th, 2018[30]. On July 26th, 2018, the FDA's advisory committee reviewed data for 60P's tafenoquine-containing product, ARAKODA™, for malaria prevention, and determined that the safety and efficacy of tafenoquine was adequate[31]. FDA itself, in a background document, noted that tafenoquine was "effective and reasonably safe", and that any additional safety concerns would be addressed through a combination of post-marketing commitments and labeling.[32] Discussion with FDA on these issues are ongoing and 60P is confident ARAKODA™ will receive marketing authorization later this year.

Thank you for the opportunity to convey an industry and scientific perspective on these issues.

Very respectfully,

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[27] 60 Degrees Pharmaceuticals LLC. 2018. Arakoda (Tafenoquine succinate) Tablets for Malaria Prevention in Adults: Briefing Document for FDA Antimicrobial Products Advisory Committee Meeting, July 26th, 2018. Accessible at: file:///C:/Users/geoff/Dropbox%20(60P)/60P%20Group%20Of%20Companies/Regulatory%20&%20Quality/UCM614202.pdf

[28] The results of the FDA audit are not available for public dissemination. GSK conclusions are summarized in GSK. 2018. Krintafel (tafenoquine succinate tablets): FDA Advisory Committee Briefing Document, July 12th, 2018. Accessible at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM612875.pdf.

[29] The transcript of this meeting has not yet been made public by FDA.

[30] See GSK press release accessible at: https://www.gsk.com/en-gb/media/press-releases/us-fda-approves-krintafel-tafenoquine-for-the-radical-cure-of-p-vivax-malaria/.

[31] The transcript of this meeting has not yet been made public by FDA.

[32] Please review the FDA's briefing document for 60P's Advisory Committee meeting, held July 26th, 2017, accessible at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM614201.pdf. This document has also been attached as an appendix to this letter.