August 28th, 2018

Dear Ms. Beverley,

Thank you for the opportunity to respond to the submissions made by Dr. Jane Quinn to the Australian Senate Inquiry into quinoline antimalarials by the Australian Defence Force (**ADF**) In reviewing the other submissions to the Inquiry we identified allegations advanced by other parties, specifically Professor McFarlane, which our prior submission does not address completely.

Dr Quinn, and Professor McFarlane have made four broad allegations about 60 Degrees Pharmaceuticals LLC and tafenoquine that are false and/or misleading. These are summarized as follows:

(i) the use of deidentified clinical trial data for regulatory submissions and pharmacovigilance analyses was unethical;
(ii) different rates of adverse event reporting in clinical trial publications and regulatory filings is evidence of medical misconduct by 60P and the ADF and requires further independent inquiry;
(iii) tafenoquine causes severe psychiatric adverse events and is not safe; and
(iv) antimalarials increase the risk of severe psychiatric events.

I am grateful for the opportunity to respond to these allegations as outlined below:

1. ***Use of deidentified data by 60P in regulatory dossiers and for pharmacovigilance reporting is appropriate:***

Dr Quinn alleges that the inclusion of clinical trial data from several studies conducted by the ADF in 60P's regulatory submissions for tafenoquine and/or for pharmacovigilance reporting is unethical because trial participants should have been reconsented.[1] ***This is false as outlined below.***

Licence requirement of trial data

The studies conducted by the ADF which Jane Quinn refers to in her submission were conducted between 2000 and 2002. 60P was not involved in these studies and was only incorporated in 2010.

In 2015, 60P entered a written license agreement with the U.S. Army Medical Materiel Development Activity (**USAMMDA**) to license information relating to tafenoquine for malaria prophylaxis to support regulatory approvals and commercialization activities. This information included administrative information, and product quality, manufacturing, non-clinical and clinical data. Some of the material

[1] SUB 16 AQVFA – Supplementary Submission pp 2-4.

licensed from **USAMMDA** included the material to which Dr Quinn refers to as "existing clinical trial data" from the ADF studies, albeit in a deidentified form as outlined below.

The license agreement between the USAMMDA and 60P contained a representation that all approvals required by regulations or law had been obtained in respect of the licensed data. Additionally, the material licensed to 60P under this Agreement contained a Consent Information Sheet which was provided to each of the ADF study participants. 60P does not hold the completed or signed consent documents.

Reconsents

Dr Quinn's reference to re-consent was expressly made in the context of informed consent given by each participant in the ADF studies (**Ethical Consent**).

However, it also raises potential issues with compliance with the *Privacy Act 1988* (Cth) (**Privacy Consent**).

Ethical Consent

In drug development it is common that deidentified data in a dossier or clinical trial data is licensed to another party. However, it is not the usualpractice to require the licensee party to obtain re-consents from the trial participants.

This would be impractical and would effectively prevent the acquisition of small pharmaceutical companies by larger ones.

In respect of the ADF studies, the trial participants consented to the ADF studies and signed a Consent Information Sheet. They were also aware of the USAMMDA's role and the fact there was a commercial sponsor to the trial.

The Consent Form for the ADF studies contained an acknowledgement that data collected as part of the studies would be kept for 75 years and:

- there was no express statement that the information would not be shared with third parties; or
- that the participants had any interest in or ability to access the data.

For these reasons 60P submits re-consents were not required as the consents are a continuation of the outcome described in the original consent.

Privacy Consent

This dossier contained deidentified trial data from clinical studies conducted by the ADF. The datasets contained DOB (date of birth) information, but the data does not allow specific individuals, who participated in those trials, to be identified by 60P.

Further, it is submitted that the trial data sets have been deidentified to the extent that the information cannot be classified as Personal Information for the purpose of the Privacy Act. Therefore, 60P does not have any obligations under the Privacy Act and the need to obtain any further re-consent of the trial participants is not necessary.

We submit the *Privacy Act* 1998 does not apply because of the way which the clinical trial data has been deidentified.

Use of Data

As outlined in our submission to the Committee dated 31 July 2018, we have been unable to confirm, based on our analysis of the TGA adverse event data, that most of the neuropsychiatric events that were alleged to have occurred in the original clinical studies actually did.[2] Furthermore, where neuropsychiatric events were reported in those clinical trials, by individuals who later also reported adverse reports to TGA, they were milder and different in scope than those described in the TGA documentation.

2. ***Independent analysis of ADF clinical trial data has already been conducted, and that analysis confirmed a similar rate of psychiatric adverse events as reported by 60P in the scientific literature and to regulatory authorities.***

Dr Quinn implies improper conduct by members of the Australian ADF and 60P, by highlighting the different ways adverse event data has been reported in the literature, and in FDA advisory committee briefing documents.[3] Dr Quinn then states that further reviews of the ADF clinical trial data by an independent group is required. ***The allegation is false and misleading for the reasons outlined below. A thorough audit and review of ADF trial data has already been conducted by an independent body.***

In a marketing application to regulatory agencies, adverse event data are systemically coded using standard medical ("MEDRA") terms, which defines each adverse event according to standardized terminology with specific system organ classes. However, there is often overlap between terms used to describe the same adverse event. For example, 'dizziness' is sometimes categorized by different clinical investigators as 'vertigo' or 'motion sickness' and might be classified under the "Nervous System" or "Ear & Labyrinth Disorder" classes depending on how it is coded. In the scientific discussion of adverse events in the literature, "neuropsychiatric events" is a catchall covering adverse events that may be reported to regulatory agencies separately as "Nervous System", "Psychiatric" or "Ear & Labyrinth Disorders". Furthermore, individual investigators, who are submitting manuscripts for publication, rather than marketing applications to regulators, are not necessarily required to report adverse event data in a prescribed format. Therefore, it is unreasonable to conclude there has been misconduct in reporting adverse events in respect of tafenoquine because the reporting of different rates of adverse events in different contexts is expected and appropriate.

Furthermore, the FDA examined the incidence of adverse psychiatric events in Study 033 and determined that it was **5.1%.**[4] The FDA also conducted independent audit of clinical trial data from Study 033. 60P, in its reporting of these data in the literature, also described an **incidence of 5.1%.**[5] Thus, an **independent regulator** has reviewed all the clinical trial data from Study 033 and concluded

[2] Our analysis of the adverse events on file with TGA can be found on pp 121, 139, 140 and 141 of the following document: 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.

[3] SUB 16 AQVFA – Supplementary Submission pp 4-10.

[4] See p45 of the following document: 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

[5] See Table 3 of Novitt-Moreno et al. *TIMD* **2017**; 17:19-27.

that the **incidence of psychiatric adverse events is the same as that reported by 60P as the Sponsor to the FDA, and in the scientific literature**. Further review by independent bodies, except in the context of additional regulatory review of marketing applications, would serve no useful purpose.

3. Tafenoquine has been found to be safe and effective by the U.S. regulator and clinical trial experience does not suggest the potential to increase the risk of serious psychiatric adverse events.

Dr Quinn asserts that tafenoquine is unsafe and increases the risk of serious psychiatric events. ***Dr Quinn's assertions are false, misleading, and neglect important facts which we summarize below:***

- On August 8th, 2018, the FDA approved tafenoquine (branded ARAKODA) for malaria prophylaxis, having previously judging it to exhibit "statistically significant prophylactic effects" and to be "reasonably safe".[6]
- It is normal practice for study investigators to attribute both a level of severity to an adverse event (mild, moderate or severe), and to assess causality (not related, not likely, possibly, probably or definitely-related to study medication). These assessments are generally not included in product labeling by regulators. However, study physicians, when making such assessments, are blinded to study treatment but have closest proximity to study participants' medical history and circumstances. The following statements about psychiatric adverse events in Study 033 are true based on blinded investigator assessment of the adverse events observed:
    - 100% of psychiatric events observed were mild or moderate.
    - 51% of psychiatric events were not-related or unlikely related to study medication.
    - 1 (representing 1 of 492 or 0.2%) of subjects were discontinued from the study due to a psychiatric event (a moderate case of depression).
- It is important to put these events in context – In any one year up to 16.5% of ADF personnel may experience a mental health condition.[7]
- U.S. prescribing information for ARAKODA includes a contraindication for those with psychotic illness.[8] However this is precautionary - it does not mean there is evidence that the approved ARAKODA dose causally increases the risk of serious psychiatric drug reactions. In fact, as noted in the label, the reason for the inclusion of the contraindication is because three clinical trial participants with an undisclosed history of psychosis experienced psychotic events while taking tafenoquine at doses different than the approved dose.[9] The label further notes that the ARAKODA clinical trial program included 3184 individuals who have taken tafenoquine at various doses, none of whom, other than three above, experienced psychosis. Furthermore, the contraindication in the U.S. prescribing information is narrow and will have limited impact on prescribing options for civilian travel and military deployment. Federal regulations in the United States prohibit enlistment or deployment of psychotic individuals. Civilian travel physicians are only rarely likely to encounter individuals with a history of active psychosis.

[6] See https://www.drugs.com/history/arakoda.html and pp 33 and 34 of 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.
[7] David Dunt. 2009. Report to Hon Alan Griffin MP and Hon Warren Snowdon MP entitled "Review of Mental Health Care in the ADF and Transition through Discharge".
[8] See p1 of prescribing information for ARAKODA at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210607lbl.pdf.
[9] See pp 1 and 4 of prescribing information for ARAKODA at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210607lbl.pdf.

- US prescribing information notes that insomnia, abnormal dreams, anxiety and depression have been observed in patients taking ARAKODA.[10] However, the same events are commonly reported during travel.[11] The U.S. prescribing information for ARAKODA also requires that physicians advise patients to seek medical advice if severe psychiatric events or moderate events, for more than three days, are experienced.[12] Since there is **no** evidence from the safety databases submitted to regulators that the approved dose of ARAKODA increases the risk of persistent or severe neuropsychiatric events relative to placebo, the correct interpretation of this additional advice in the label is that it is precautionary. It serves to ensure a traveler seeks medical advice if they experience adverse psychiatric events that do not ordinarily occur during travel.

4. ***Antimalarial drugs do not increase the risk of long-term severe psychiatric events even in stressful situations.***

Professor McFarlane speculates in his testimony that antimalarial drugs that are psychotropic may increase the risk of PTSD and other serious psychiatric conditions.[13] Since our original submission does not address these issues in their entirety, we have taken the opportunity to respond as outlined below:

- It is not disputed by most travel physicians that mefloquine at prophylactic doses statistically increases the risk of the following adverse events relative to doxycycline and atovaquone-proguanil: insomnia, abnormal dreams, anxiety and depression.[14] Professor McFarlane speculates that antimalarial drugs that are "psychotropic" and cause such events in some individuals might increase the risk of rarer and more severe post-deployment psychiatric events, particularly in stressful situations[15]. However, he neglects to mention that, at a population level, the scientific literature does not support such a causal association in practice. In fact, recent reports from reputable U.S. government agencies have demonstrated that (i) deployment and combat experience not antimalarials increases the risk of PTSD and other serious psychiatric events, (ii) mefloquine and atovaquone-proguanil result in a similar increase in the total burden of neuropsychiatric illness during deployment and (iii) the long term risk of serious psychiatric events is not increased for mefloquine relative to other antimalarial prophylactics if prescribing information is followed.[16]

Summary and Conclusions:

The allegations described at the start of this letter are false and/or misleading.

The allegations are false because they do not correctly represent the factual situation. The allegations are misleading because they are not substantiated by the significant body of medical and scientific evidence, which has been gathered over a period of time and accepted by the FDA in approving ARAKODA.

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[10] See pp 1 and 4 of prescribing information for ARAKODA at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210607lbl.pdf.
[11] Overbosch. J Travel Med 2003; 10 Suppl 1:S16–S20.
[12] See p19 of prescribing information for ARAKODA at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210607lbl.pdf.
[13] See Submission 58, p2.
[14] See Tickell Painter et al. *Cochrane Database Syst Rev* **2017**; 10:CD004791.
[15] See Submission 59, p2.
[16] See Eick-Cost et al. *Am J Trop Med Hyg* **2017**; 96:159-166, Tan et al. TMID 2017:17:50-55 and Schneiderman et al Am J Trop Med Hyg. 2018 Jun 25. doi: 10.4269/ajtmh.18-0107.

While Dr. Quinn, Professor McFarlane and others may sincerely believe they are assisting veterans with their advocacy, there is a real risk that their efforts will unnecessarily scare the public and taint the reputation of an important new tool in the global effort to eradicate malaria. **Millions of lives may be lost if tafenoquine becomes unusable due to their efforts.**

60P hopes that the Committee will carefully consider the information sourced from the independent scientists who have provided submissions, and who overwhelmingly believe that tafenoquine is safe and will make an important contribution to malaria eradication efforts. 60P urges the Committee not to make any recommendations that would undermine this important global effort.

Very respectfully,

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