Additional information regarding ADF Army Malaria Institute clinical trials adverse event reporting for the drug tafenoquine.

Submission to the Senate Inquiry 'Investigation into the use of the quinoline antimalarial drugs mefloquine and tafenoquine in the Australian Defence Force.'

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This submission is made on behalf of the Australian Quinoline Veterans and Families Association by Associate Professor Jane Quinn (BSc Hons, PhD), Charles Sturt University.

In addition to my previous submission, this document will consider new evidence relevant to the Terms of Reference of this Senate Inquiry:

A - (a): identifying and reporting adverse drug reactions from quinoline anti-malarial drugs among ADF personnel.

In my previous submission I presented recent information related to an application by the pharmaceutical company GlaxoSmithKline (GSK) for registration of tafenoquine for radical cure. This information clearly identified an adverse event profile for tafenqouine that had not been reported fully at the time of the Australian Defence Forces (ADF) Army Malarial Institute (AMI) orchestrated clinical trials, and showed that GSK had included information relating to long term adverse events in their submission to the American regulator body in their registration application submission. This meeting took place on the 12th July 2018, the outcome of which was that tafenoquine was accepted for registration in the United States (US) for radical cure in patients between 18 and 65 years, with acceptable proof of efficacy, and 'adequate' proof of safety. Patient safety information for tafenoquine for this use will be required to include a contraindication for use in patients with a known history of psychiatric disorders, similar to the related drug mefloquine. The successful registration of tafenoquine for radical cure awarded GSK a FDA Priority Review Voucher, with an estimated value on resale of $100-350 million US dollars.

Even more recently, on 26 July 2018, the Australian pharmaceutical company 60 Degrees Pharmaceuticals Ltd Pty (60P) underwent review of their FDA application to the Antimicrobial Drugs Advisory Committee (ADMAC) for the registration of tafenoquine under the name 'ARAKODA' for the purposes of antimalarial prophylaxis in patients aged between 18 and 65. 60P are currently undertaking trials to develop data sufficient for registration in children, information which it indicated would be submitted to the FDA separately to their current submission for prophylaxis.

The briefing document presented to the FDA in support of the 60P application for tafenoquine for malarial prophylaxis contained some information of great relevance to this Senate Inquiry, specifically, a review of adverse event data collected during the trial identified as '033' which was the trial in which ADF members were participants and tafenoquine was compared to mefloquine for malarial prophylaxis. This study was discussed

in detail in my first submission to this Inquiry and was reported in the following publications (Edstein, Walsh et al. 2001, Nasveld, Edstein et al. 2010).

When considering the document presented by 60 Degrees Pharmaceuticals to the FDA, the information of critical importance to this Inquiry are that e**vidence published in the 60P ADMAC dossier clearly shows that:**

1) **Adverse events related to exposure to tafenoquine in ADF members were significantly underreported in the publications relating to the original trials resulting in the significance of these events being down-played for two decades, and;**
2) **Participants trial data has been shared with a 3rd party without full disclosure to the trial participants, and;**
3) **Re-examination of trial data has occurred by a third party without re-consent.**

Evidence supporting these statements is contained in the 60P briefing document. A full copy of the report can be accessed at:

https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM614202.pdf

The specific extracts identifying this information will now be identified.

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'1.5. Tafenoquine Product History
Tafenoquine has been developed as a government-private partnership with the United States Army Medical Material Development Activity (USAMMDA), the Walter Reed Army Institute of Research (WRAIR), and GlaxoSmithKline (GSK). In 2009, USAMMDA and GSK agreed to separate the responsibilities for filing the prevention and treatment dossiers respectively. ***USAMMDA has subsequently licensed the prevention indications for tafenoquine to 60 Degrees Pharmaceuticals LLC (60P) with a subsidiary in Australia (60 Degrees Pharmaceuticals Australia Pty Ltd) while GSK retains the treatment indication for Plasmodium vivax (Pv) malaria.****'*

(*emphasis added*)

Firstly, the product history of tafenoquine development by GSK and the USAMMDA clearly identifies the time at which the interests of GSK and USAMMDA diverged to separate the two uses of tafenoquine – radical cure and prophylaxis – into separate dossiers for continued

development to market. GSK and USAMMDA were both co-sponsors of the original ADF AMI-run trial administered by AMI scientists in East Timor in 2000 – 2001 involving 654 participants from 1st Royal Australian Regiment (1RAR), of which 492 were given tafenoquine and 162 given the comparator drug mefloquine. This trial is described as a 'pivotal' trial in non-immune subjects and was designated Trial '033' by GSK and their trial collaborators.

What is critical in regard to the sublicensing information described above is that, as a co-sponsor, and holder of the overarching human research ethics protocol for the trial, it would be normal to assume that, as a financial sponsor, the Australian Defence Force should have been consulted with regard to this license transfer as this would also require the transfer of existing clinical trial data to the new licensee. The specific relevance of this information is that, in the event that a transfer was agreed, trial documentation and evidence would then be shared by a third party not originally involved in the trials themselves – in this case 60 Degrees Pharmaceuticals.

It is possible that the transfer of confidential information breaches the now current standard of ethical requirement in the ADF where any information related to past clinical trials – by instruction from a Defence Communication (DEFCOM) circulated in 2016 – must undergo a re-consent process with the original trial participants if that information is to be reused or re-examined. Once would logically assume this should also apply if the original trial information was to be utilised by a third party not originally involved in the study or approved as a participant in the original Army Human Research Ethics Committee application. **As such the question arises whether the transfer of trial participant information and the reassessment of trial '033' participant data would represent a breach of research ethics in relation to this trial documentation**.

Secondly, is it possible to conclude that individual participant information related to trial '033' have been accessed by 60 Degrees Pharmaceuticals? Yes. Information related specifically to reanalysis of individual participant data has been included as part of their ADMAC application. The sponsors, 60P, clearly articulate that a re-review of participant information had occurred recently, and prior to their submission to the FDA in the following sections of their ADMAC submission:

On p121 they state:

12.7.6.4. Neuropsychiatric Adverse Events Reported to the Australian Therapeutic Goods Administration (TGA) Related to Study 033 in Australian Military Personnel
Between February 18th and 23rd, 2017, a total of 17 cases referencing tafenoquine and involving potential neuropsychiatric AEs were reported to the Australian Therapeutic Goods Administration (TGA). ***GSK shared information internationally for 4 of these 17 cases in the form of 4 IND Safety Reports (INDSR), which were provided to the Sponsor and to all investigators worldwide on 08 June 2017****. GSK indicated that the four INDSR referred to four of their CSD Safety Database Numbers. Details of these 4 cases are provided in Appendix A, Table 56, which summarizes the AE information that was reported to the TGA for each subject and compares this information to the trial safety information that is contained in the Sponsor's database. Based on Sponsor's information, 1 of the 4 subjects had no neuropsychiatric ARs reported during the study, while 2 of the subjects had only mild symptoms (motion sickness/vertigo or anxiety) that were considered to be unrelated to tafenoquine. Only one subject had AEs (mild abnormal dreams and mild-moderate insomnia) that were suspected of having a relationship to the study drug. However, these sleep disturbances began on Study Day 0 and occurred in the context of the subject's ongoing back pain (present at enrolment) and new onset shoulder pain that were concurrent medical problems during the trial.*

Aside from the 4 subjects described above, there were 12 additional subjects with TGA reports whose identification information was limited to date of birth (DOB). ***By using DOB, 8 of these 12 subjects were tentatively matched to a subject who had participated in Study 033****. Only 1 of the 8 DOB-matched subjects had any psychiatric AEs reported during Study 033. This subject reported 15 days of lethargy/somnolence that began 4 days after he received his final tafenoquine dose and coincided with his post-deployment return home. Notably, the subject also reported AEs of "increased appetite", "increased thirst", and "nausea" for the same 15 days during this same post-deployment period. In contrast, no lethargy/somnolence was reported by this subject during his 27 weeks of tafenoquine dosing.*

(***emphasis added***)

Irrespective of the conclusions made above, these statements by 60P clearly suggest that original trial participant data was shared with them, presumably as part of the licencing agreement from GSK and USMMADA. Whether this was approved through the ADF Human Research Ethics Committee is a question that needs to be answered given the recent directive for re-consent prior to reanalysis of existing trial data for these studies.

The sponsor, 60P then further expand on their re-analysis of the trial '033' data:

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*'****A review of psychiatric data from Study 033*** *revealed that the military subjects in that study had a unique psychiatric AE profile compared to subjects in other Tafenoquine ACR studies due to the combat environment to which these soldiers were exposed (Section 12.7.6.1). Compounding this psychologically hostile environment were the many physical insults and injuries which the soldiers experienced as a result of their warlike deployment (Table 48).* ***However, in spite of the stressful environment to which the Tafenoquine ACR Deployed subjects were exposed, the incidence of psychiatric AEs in the Deployed ACR population***

was only 5.1%, with the majority of psychiatric AEs assessed as mild (84.4%) and considered not related or unlikely related to the study drug (52.0%).

(***emphasis added***)

This newly reported rate of 84.4% neuropsychiatric AEs, (of which the investigators conveniently dismiss 52% as unlikely to be related to drug exposure) indicated that **32.4% of trial participants experienced a neuropsychiatric side effects that the investigators considered to be causally related to drug exposure yet was clearly not reported by the trial investigators,** either in the publication subsequent to the trial or in any subsequent meta-analysis of this data (Novitt-Moreno, Ransom et al. 2017).

To further compound this extraordinary omission, 60P proceed to suggest a rationale for this dramatically increased rate of neuropsychiatric AE's (other than a failure of the investigators to openly report the actual trial data) compared to other trial populations studied:

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Among ADF personnel deployed to East Timor, independent research has indicated that 7.2% eventually developed symptoms of post-traumatic stress disorder (PTSD) and 6.9% had a long-term high level of psychological stress, based on data gathered in 2007-2009 (7-9 years after deployment) (Waller-2012).

Overall, these findings support the hypothesis that the environment to which Tafenoquine ACR subjects and Mefloquine subjects in Study 033 were exposed was a psychologically hostile environment that could potentially foster the development of neuropsychiatric AEs (Novitt-Moreno-2017). This same effect was documented in a similar population of ADF peacekeeping forces in East Timor who took part in a study of mefloquine versus doxycycline (Kitchener-2005)…….

Reports from troops deployed during this time suggest that this deployment was not significantly more stressful than others they had experienced, and a more likely suggestion for the increased rates of PTSD identified by Waller and colleagues is that that these were likely misdiagnosed cases of chronic quinoline encephalopathy related to their drug exposure. The comparison to 'non-deployed' individuals is also misleading as these data are derived from different trial populations, not those within trial '033' and therefore represent individuals with a very different ethnic background (see Table 49 below).

p115: Table 48

Deployed subjects accounted for the majority of subjects with psychiatric AEs in both the Tafenoquine ACR and Mefloquine populations, representing ***25 (78.1%) of 32 in the Tafenoquine ACR group*** *and* ***7 (70.0%) of 10 in the Mefloquine group****. Among both the Deployed Tafenoquine ACR and Deployed Mefloquine populations, the majority of psychiatric AEs (84.0% and 85.7%, respectively) were assessed as mild, and the majority were considered not related or unlikely related to the study drug (52.0% and 57.2%, respectively).*

It is very clear from information provided by two FOI requests to the TGA requesting information on adverse events reported at the time of trial '033' (RightToKnow 2018a, RightToKnow 2018b) that these adverse events were clearly not reported to the relevant authorities: mefloquine (7 reports) an tafenoquine (25 reports) (Nasveld reference 2010).

Finally, novel data not previously shown in the study publications are identified below (Tables 49-52, 60P ADMAC submission, 26th July 2018). In Table 49, 60P clearly identify that 84% and 85.7% of participants reported mild psychiatric AE's for tafenoquine and mefloquine respectively Original study publication reported 13% and 14.2% neuropsychiatric side effects respectively (Nasveld, Edstein et al. 2010). Of these, 60P indicate that 44% and 42.9% were *possibly* causally related to drug exposure. Conveniently, they suggest none of the moderate neuropsychiatric AE's reported (16% for tafenoquine and 14.3% for mefloquine) to be causally related. Given that this AE data has been suppressed until now, whether this latter claim can be believed without independent review is open to speculation.

Table 49: Psychiatric AEs, Severity Grade and Relationship to Study Drug, Tafenoquine ACR Group vs Placebo and Mefloquine

		Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR)			Mefloquine 250 mg daily x 3 days, then 250 mg weekly		
	Placebo (n=396)	Total ACR Population (n=825)	Deployed Subjects in Study 033 (n=492)	Non-Deployed Subjects (n=333)	Total Mefloquine Population (n=309)	Deployed Subjects in Study 033 (n=162)	Non-Deployed Subjects (n=147)
Total Number (%) of Subjects with Psychiatric AES	3 (0.8%)	32 (3.9%)	25 (5.1%)	7 (2.1%)	10 (3.2%)	7 (4.3%)	3 (2.0%)
AE Severity							
Total No. of Subjects Reporting AEs	3	32	25	7	10	7	3
Mild	2 (66.7%)	27 (84.4%)	21 (84.0%)	6 (85.7%)	8 (80.0%)	6 (85.7%)	2 (66.7%)
Moderate	1 (33.3%)	4 (12.5%)	4 (16.0%)	0	1 (10.0%)	1 (14.3%)	0
Severe	0	1 (3.1%)	0	1 (14.3%)	1 (10.0%)	0	1 (33.3%)
AE Relationship to Study Drug: Psychiatric AEs							
Total No. of Subjects Reporting AEs	3	32	25	7	10	7	3
Not Related	0	10 (31.3%)	9 (36.0%)	1 (14.3%)	4 (40.0%)	3 (42.9%)	1 (33.3%)
Unlikely	2 (66.7%)	8 (25.0%)	4 (16.0%)	4 (57.1%)	2 (20.0%)	1 (14.3%)	1 (33.3%)
Possibly	1 (33.3%)	13 (40.6%)	11 (44.0%)	2 (28.6%)	4 (40.0%)	3 (42.9%)	1 (33.3%)
Probably	0	1 (3.1%)	1 (4.0%)	0	0	0	0
Definitely	0	0	0	0	0	0	0

The novel data reported in the 60P ADMAC submission is further dissected. They go on to suggest:

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'Among the 25 deployed ADF subjects who experienced psychiatric disorders, the majority [18 (72%) of 25] developed problems impacting sleep (insomnia, abnormal dreams, nightmares, sleep disorder). In comparison, among non-deployed subjects, sleep AEs affected only 3 (43%) of 7 subjects with psychiatric AEs. This finding that sleep-related AEs impacted deployed military subjects underscores the potentially dramatic effect that deployment can have on sleep in military populations.'

The latter statement is bizarre in the extreme. Only a comparison between deployed subjects receiving the trial drug compared to those receiving placebo could possibly inform this hypothesis. Clearly as this comparison was not undertaken in trial '033', or in any of the other studies reported and as such the implication that sleep-related AE's were only related to deployment and not to drug exposure clearly cannot be validly argued. What is most important about this new information is that the profile of sleep-related AE's also clearly fits that of the comparator drug mefloquine (see Table 47 below), in which sleep abnormalities and abnormal dreaming are now clearly identified as common symptoms potentially prodromal to more serious chronic adverse events (Nevin 2012, Nevin 2015, Nevin 2017).

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Table 47: Summary of Psychiatric Adverse Events: Tafenoquine ACR Group versus Placebo and Mefloquine

	Number (%) of Subjects		
	Tafenoquine 200 mg daily x 3 days, then 200 mg weekly (ACR) (n=825)	**Placebo (n=396)**	**Mefloquine 250 mg daily x 3 days, then 250 mg weekly (n=309)**
Included Studies	**030, 033, 043, 045, 057**	**030, 043, 044, 045, 057**	**030, 033, 045**
Number (%) of Subjects with Psychiatric AEs leading to Discontinuation			
Anxiety	0	0	1 (0.3%)
Depression	1 (0.1%)	0	0
Suicide attempt	1 (0.1%)*	0	0
Number (%) of Subjects with Psychiatric SAEs			
Anxiety	0	0	1 (0.3%)[a]
Suicide attempt	1 (0.1%)[a]*	0	0
Psychiatric AEs Occurring in ≥1% of Study Subjects			
Insomnia	10 (1.2%)	3 (0.8%)	1(0.3%)
Psychiatric AEs Occurring in ≤1% of Study Subjects			
Abnormal dreams	5 (0.6%)	0	2 (0.6%)
Sleep disorder	3 (0.4%)	0	2 (0.6%)
Nightmare	3 (0.4%)	0	1 (0.3%)
Depression	2 (0.2%)	0	1 (0.3%)
Agitation	2 (0.2%)	0	0
Anxiety	0	0	2 (0.6%)
Anxiety Disorder	2 (0.2%)	0	0
Euphoric mood	2 (0.2%)*	0	0
Bipolar disorder	1 (0.1%)*	0	0
Depressed mood	1 (0.1%)*	0	0
Neurosis	1 (0.1%)	0	0
Panic attack	1 (0.1%)*	0	0
Stress	1 (0.1%)*	0	0
Suicide attempt	1 (0.1%)*	0	0
Somnambulism	0	0	1 (0.3%)
Loss of libido	0	0	1 (0.3%)

[a]SAE led to discontinuation
*Indicates that all AEs in this category were considered unrelated or unlikely related to tafenoquine. Categories with no asterisk included some AEs that were considered possibly or probably related to tafenoquine.

Table 47 provides a detailed breakdown of psychiatric AEs. This newly reported evidence clearly identifies a range of neuropsychiatric adverse events that have not been previously published, or reported to the appropriate regulatory authorities or in the scientific literature to date. The reasons for this are unclear but may potentially relate to this information being unfavourable for potential registration of the product.

Although this data presented above encompasses additional participant data to that of trial '033', that tafenoquine and mefloquine exhibit the same neuropsychiatric adverse event profile in relation to sleep disorders and insomnia, and that additional cases of 'anxiety' were reported, suggests that tafenoquine does not have as benign adverse event profile as the sponsors would like us to believe. It would therefore be prudent to assume that those prodromal AEs similar to mefloquine (insomnia, sleep disorders, abnormal dreams, nightmares (Nevin 2015)) be considered comparable to those experienced by persons taking mefloquine for malarial prophylaxis.

In their ADMAC application the sponsors 60P suggest that the incidence of sleep disorders in both trial populations was causally related to 'other' coincident medical conditions and not drug exposure. This is a spurious argument given the known AE profile of melfoquine and its relationship with abnormal sleep and dreaming. These statements therefore appear more a tactic to divert attention from the data than to suggest a plausible argument for tafenoquine's identified AE profile. In support of this conclusion, these arguments were also not totally believed by the FDA panel assessing the 60P submission, who failed to pass a unanimous vote for safety for tafenoquine for prophylactic use and expressed significant concerns about its neuropsychiatric adverse event profile at the ADMAC review meeting on the 26th July 2018.

In Conclusion

Evidence presented in the 60 Degrees Pharmaceuticals application to the US FDA for registration of tafenoquine for use in malarial prophylaxis identifies a clear and consistent adverse event profile with a high degree of similarity to that subsequently reported by ADF veterans involved in the GSK / USMAADA / ADF AMI trials. The dossier also indicated that adverse event data reported in the publications associated with the trial downplayed the incidence of neuropsychiatric AE's, obscuring that information from public view for nearly two decades.

Recommendations:

- **That a full and thorough investigation is undertaken in to the licencing of tafenoquine to 60 Degrees Pharmaceuticals;**
- **That an independent analysis of all trial data generated by AMI for Trial '033' be undertaken, after re-consent or waiver of consent by trial '033' participants, to validate and confirm the AE data presented in the 60P ADMAC submission to ensure that this data has now been fully and correctly reported.**

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