**Five Minutes with Dr Remington Nevin**
**Interview Transcript**

**To start off with, when it was announced that Tafenoquine had been approved by the FDA, what was your initial reaction?**

This was not at all surprising. Every drug that is eventually banned in the US, or that receives a strong boxed warning, was once deemed safe and effective by the FDA and its advisory committees. Mefloquine is a good example of this. Thirty years ago, the advisory committee reviewing the New Drug Application for mefloquine was not even made aware that mefloquine prophylaxis could have psychiatric adverse effects. Had the committee at the time considered evidence of the risks from structurally-related drugs, it likely would have been much more critical in its evaluation.

I believe the advisory committee and FDA similarly erred in their review of tafenoquine in not considering strong evidence of the dangers from similarly structurally-related drugs. I expect that in due course, the advisory committee and FDA will reconsider its conclusions. The recent 9-4 split vote on the safety of tafenoquine for prophylaxis is perhaps an early indication of this. Unlike mefloquine, for which it took 30 years for its neurotoxicity to be recognized, I expect that for tafenoquine, the time to recognition of its dangers will be measured in months or years, not decades.

**It's fair to say that you are very vocal about your concern for drugs like Tafenoquine, and Mefloquine which you mentioned there. What sort of message do you hope to share?**

As someone who has extensive training in tropical and preventive medicine, I recognize the critical importance of antimalarial drugs. My work, and that of our foundation, is focused on the unique safety risks of the quinoline antimalarial drugs. This is a class of drug with inherent CNS toxicity, whose use is very likely contributing significantly to the global burden of mental illness and neuropsychiatric disability. We believe that if drugs of the quinoline class are to continue to be used in global malaria control efforts, greater consideration must be given by the malaria community to identifying and understanding these effects. All too often, neuropsychiatric adverse effects of antimalarial drugs are trivialized by prominent malariologists. I was recently at my alma mater, the Johns Hopkins Bloomberg School of Public Health, where a discussion of possible neuropsychiatric adverse effects from piperaquine and chloroquine was met with derisive laughter by the audience. This needs to change. It makes no sense to work to eliminate the burden of global disability due to malaria, only to risk replacing it with

disability due to neuropsychiatric illness. This is a real possibility with the large-scale use of neurotoxic quinoline antimalarial drugs.

**Right, but I one thing that stood out to me about your message is that you have said in the past that the main reason for why drugs companies are producing tafenoquine is because of financial gain. Could you expand on what you mean by this?**

It should come as no surprise to the malaria community that drug companies are primarily motivated by profit and their fiduciary responsibility to their shareholders, and this fact is demonstrated clearly in the development of tafenoquine. This drug had languished in the U.S. military's drug development program for decades and had been nearly abandoned prior to FDA's introduction of the Priority Review Voucher (PRV) incentive in the late 2000s. 60 Degrees was formed by ex-U.S.-military-affiliated personnel who had strong personal and professional connections to the military's drug development community, and monetization of a PRV appears to have been a large part of the company's business plan. The CEO of 60 Degrees had all but bragged that earning a PRV for Tafenoquine's approval could earn his newly-formed company up to $350 million.

Similarly, for GSK, the economics of bringing tafenoquine to market in the U.S. do not make much sense outside of the PRV incentive. The domestic market for tafenoquine for the strict indication of radical cure (as opposed to presumptive anti-relapse treatment) of P. vivax  is only a few hundred patients a year, which would translate into far less than $1 million in annual sales. While GSK's development of tafenoquine has been incentivized by financial arrangements with non-profits, and by the opportunity to market the drug in the developing world (likely at minimal profit), the incentives from the PRV appear to be the main financial motivation. The favorable media attention GSK earns from its development of tafenoquine, which reflects well on its other profit-making activities, is also likely a strong related consideration.

**It's been in the news recently that some US Veterans are suffering from long term side effects after taking anti-malaria drugs, like Mefloquine. How does it make you feel now that Krintafel has been approved?**

The approval of tafenoquine was a pyrrhic victory for those would deny the CNS toxicity of the quinoline class, a property that has adversely affected the health of US veterans since the widespread use of synthetic quinolines in World War II. In order to argue the need for tafenoquine as prophylaxis, for example, the sponsors had to acknowledge the

neurotoxicity of mefloquine as justification for its development. Similarly, in comparing the safety profile of tafenoquine to that of primaquine, the sponsors may have unwittingly directed future attention to a hidden epidemic of poisoning by this drug.

Primaquine, like all of the nearly 140 members of the 8-aminoquinoline class appropriately tested in animal models, has been found to be neurotoxic and to cause injury to the CNS. Although primaquine has been considered exceptionally safe by the malaria community on the basis of seemingly reassuring pharmacovigilance experience, consideration must be given to the fact any adverse effects from primaquine are likely to have been misattributed to chloroquine and mefloquine, which are almost always co-administered with it, or even to the presumed neuropsychiatric effects of malaria, which we recognize today are much more limited than our prior conceptions. For these reasons, I expect the widespread deployment of tafenoquine, particularly as monotherapy, will speed the malaria community's recognition of CNS neurotoxicity as a class effect of the quinolines, affecting not just tafenoquine, primaquine, and the other 8-aminoquinolines, but the 4-aminoquinolines including chloroquine and piperaquine, and in fact, all other subclasses of antimalarials which share the quinoline core.

**You run a foundation called the Quinisim Foundation. Could you give us some information behind the name?**

Quinolines are particularly toxic to the CNS, and when tested in appropriate animal models, poisoning by drugs of this class cause a unique and highly specific pattern of injury to the brainstem and limbic system. In human use, these drugs are associated with a risk of permanent neuropsychiatric disability, whose signs and symptoms reflect the localization of this observed CNS injury.  A condition with a known cause and pathophysiology, and recognizable signs and symptoms, is a disease. Up until recently, this disease has lacked a name. Our foundation has given this disease a name: chronic quinoline encephalopathy, otherwise known as neuropsychiatric quinism. Our foundation has repurposed the once-obsolete term quinism, which had previously been synonymous with cinchonism, to define the more general family of medical disorders caused by quinoline poisoning. Quinine, from which both quinoline and quinism take their names, is of course, the prototypical drug of the class. Our foundation's logo emphasizes the fundamental importance of the quinoline core in the toxicity of all antimalarial drugs of this class.

**And what do you hope to achieve?**

We promote and support education and research on the family of medical disorders caused by quinoline poisoning, but in practice, at the moment our work is focused on neuropsychiatric quinism. Fundamentally, we seek to draw attention to the hidden epidemic of disability caused by quinoline poisoning.  In due course will we expand our focus to global populations affected by quinism, but in the near-term our work is focused particularly among veterans. We are working assist healthcare organizations to identify those exposed to quinolines and to screen for symptomatic quinoline exposure, and to assist government agencies to recognize those suffering disability from quinism. We must also educate clinicians to diagnose chronic quinoline encephalopathy and other medical conditions caused by quinoline poisoning, and to train researchers to distinguish the effects of neuropsychiatric quinism from those of other disorders, including Post-traumatic Stress Disorder (PTSD) and Traumatic Brain Injury (TBI). We also seek to study the global epidemiology of this condition and support a search for effective treatments.