ABSTRACT:

The 2-aminopyridine MMV048 was the first drug candidate inhibiting Plasmodium phosphatidylinositol 4-kinase (PI4K), a novel drug target for malaria, to enter clinical development. In an effort to identify the next generation of PI4K inhibitors, the series was optimized to improve properties such as solubility and antiplasmodial potency across the parasite life cycle, leading to the 2-aminopyrazine UCT943. The compound displayed higher asexual blood stage, transmission-blocking, and liver stage activities than MMV048 and was more potent against resistant Plasmodium falciparum and Plasmodium vivax clinical isolates. Excellent in vitro antiplasmodial activity translated into high efficacy in Plasmodium berghei and humanized P. falciparum NOD-scid IL-2Rnull mouse models. The high passive permeability and high aqueous solubility of UCT943, combined with low to moderate in vivo intrinsic clearance, resulted in sustained exposure and high bioavailability in preclinical species. In addition, the predicted human dose for a curative single administration using monkey and dog pharmacokinetics was low, ranging from 50 to 80 mg. As a next-generation Plasmodium PI4K inhibitor, UCT943, based on the combined preclinical data, has the potential to form part
of a single-exposure radical cure and prophylaxis (SERCaP) to treat, prevent, and block the transmission of malaria.