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UCT943, a next-generation plasmodium falciparum PI4K inhibitor preclinical candidate for the treatment of malaria

Brunschwig C
Lawrence N
Taylor D
Abay E
Njoroge M
Basarab GS
Le Manach C
Paquet T
Cabrera DG
Mancama, Dalubuhle T

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-2Rγnull* 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.