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NOVEL ANTIMALARIAL COMPOUND ACT-451840: PRECLINICAL ASSESSMENT

Addressing the urgent need for the development of new antimalarials, a chemical class of potent antimalarial compounds with a novel mode of action was recently identified. Here, the preclinical characterization of one of these compounds, ACT-451840, conducted in partnership with academic and industrial groups is presented. The properties of ACT-451840 are described, including its spectrum of activities against multiple life cycle stages of the human malaria parasite Plasmodium falciparum (asexual and sexual) and Plasmodium vivax (asexual) as well as oral in vivo efficacies in two murine malaria models that permit infection with the human and the rodent parasites P. falciparum and Plasmodium berghei, respectively. In vitro, ACT-451840 showed a 50% inhibition concentration of 0.4 nM against the drug-sensitive P. falciparum NF54 strain. The 90% effective doses in the in vivo efficacy models were 3.7 mg/kg against P. falciparum and 13 mg/kg against P. berghei. ACT-451840 potently prevented male gamete formation from the gametocyte stage with a 50% inhibition concentration of 6 nM and dose-dependently blocked oocyst development in the mosquito with a 50% inhibitory concentration of 30 nM. The compound's preclinical safety profile is presented and is in line with the published results of the first-in-man study in healthy male participants, in whom ACT-451840 was well tolerated. The fast parasite reduction ratio (PRR) and gametocytocidal effect of ACT-451840 were recently also confirmed in a clinical proof-of-concept (POC) study.

Biography

Sergio Wittlin is a group leader at the Swiss Tropical and Public Health Institute (Swiss TPH). He received his PhD in biochemistry from the Biozentrum of the University of Basel, Switzerland in 1999 and obtained a 3 years of postdoctoral experience in molecular genetics at the Walter and Eliza Hall Institute at Melbourne, Australia. In 2002 he moved to the Swiss TPH, where his research is focused on the malaria parasite in cell culture assays and mouse models, with the ultimate aim to discover new antimalarial drugs in a multidisciplinary approach. In 15 years of collaboration with the Medicines for Malaria Venture (MMV) in Geneva, his laboratory was significantly involved in moving 4 compounds in the MMV pipeline into clinical trials.

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