Drugs for treatment and prevention, and other novel therapies

OC - (8415) - A TRANSLATIONAL PRECLINICAL PLATFORM TO ASSESS THE CHEMOPROPHYLAXIS AND CHEMOPREVENTION DOSE-RELATIONSHIP OF MALARIA DRUGS: THE CASE STUDY OF M5717

Rebelo, Sofia (Portugal); Simão, Daniel (Portugal); Arez, Franscisa (Portugal); Fontinha, Diana (Portugal); Machado, Marta (Portugal); Martins, Tatiana (Portugal); Fischli, Christoph (Switzerland); Oeuveyor, Claude (Switzerland); Carrondo, Manuel (Portugal); Rottman, Matthias (Switzerland); Spangenberg, Thomas (Switzerland); Brito, Catarina (Portugal); Greco, Beatrice (Switzerland); Prudencio, Miguel (Portugal); Alves, Paula M (Portugal)

1 - Instituto de Biologia Experimental e Tecnológica; 2 - Instituto de Medicina Molecular; 3 - Swiss Tropical and Public Health Institute; 4 - Merck Global Health Institute

Major progresses have been made in the control of malaria leading to significantly reduce the number of cases and death. However to reach the elimination stage, new tools will be needed, including combination of drugs capable of blocking the spread of malaria through chemoprophylaxis.

M5717 is a first-in-class compound that targets the Plasmodium Eukaryotic translation Elongation Factor 2, essential for protein synthesis. M5717 is highly potent against all developing stages of Plasmodium parasites and has a long half-life suggesting that a single dose development may be possible for cure, prophylaxis and transmission blocking activities. In vivo preclinical PK/PD data indicates an increased exposure in the portal vein compared to peripheral circulation translating into a prophylactic activity at a lower dose than the curative one. M5717 is currently completing first-in-man studies with the objective of initiating clinical prophylactic development in 2019. Additional data to model the human prophylactic dose will be needed prior to initiate the studies to demonstrate clinical efficacy (Phase 2).

We recently established a human cell-based platform for drug screening against Plasmodium liver-stage infection relying on human hepatic 3D cultures in bioreactors supporting rodent P. berghei infection with rate of infection and parasite development similar to existing models. The platform was validated by assessing the activity of currently used antimalarial drugs.

Here we report the data of a dose response experiment to establish the liver stage efficacious concentration of M5717 compared to atovaquone in Plasmodium-infected hepatic 3D cultures. The data obtained is this new model were confirmed using the in vivo model of P. berghei sporozoite-induced infection in mice, demonstrating the validity of the Plasmodium-infected hepatic 3D cultures as an enabling technology for malaria drug development. These data are also providing additional evidences that M5717 should be developed as a chemoprophylactic agent for the prevention of malaria.