Title: Simulations to investigate new Intermittent Preventive Therapy Dosing Regimens for Dihydroartemisinin-Piperaquine

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Objectives: A fix combination of dihydroartemisinin (DHA)-piperaquine (PQ) has been suggested as a new alternative for Intermittent Preventive Therapy (IPT) in response to the emergence of resistance to other treatment alternatives [1]. This project aim to explore alternative dosing regimens for DHA-PQ to those studied in clinical trials by the application of simulations with a PKPD model.

Methods: A time-to-event model characterizing the concentration-effect relationship for the malaria preventive effect of DHA-PQ has been developed [2-3] in application to a study of 1000 healthy male subjects in Northern Thailand [1]. The clinical trial featured treatment regimens with DHA-PQ dosing on three consecutive days repeated every month or every second month. Simulations based on the PKPD model have been used to compare the clinical utility of these regimens to novel regimens primarily based on once weekly dosing. The benefit of an initial loading dose strategy was investigated both for monthly and weekly dosing regimens. All scenarios were simulated under the assumption of different levels and patterns of treatment compliance (100%, 80% and 60%). All simulations were carried out using the software Berkeley Madonna.

Results: Assuming perfect compliance a weekly dosing regimen with an initial 3 day loading dose session was predicted to result in a yearly malaria incidence of less than 1 %, compared to approximately 3% for the once monthly dosing regimen and 52% for placebo. Assuming on average 80% compliance the weekly dosing regimen maintained the incidence below 1% whereas the incidence for a monthly regimen would increase to 8%. In case of very poor compliance (60%) the weekly dosing regimen was predicted to result in a 3% incidence compared to >15% for any monthly regimen.

Conclusions: Simulations with a PKPD model for the malaria preventive effect of DHA-PQ was useful in investigations of alternative dosing regimens. A novel weekly dosing regimen was indicated to outperform the previously suggested monthly regimen especially with regards to being less sensitive to poor compliance.

References:

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