Clinical development of antimalarial combination regimens:

Pharmacokinetic and pharmacodynamic evaluation of novel multi-drug antimalarial treatment regimen in clinical phase II and III trials in sub-Saharan Africa

Acronym: SPAP-PK

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Background and preliminary data: Malaria remains a major public health issue in sub-Saharan Africa, accounting for about 90% of global cases and about 600,000 deaths annually. Artemisinin-based combination therapies (ACTs), administered over three days, show high efficacy in clinical trials but are less effective in routine use due to challenges in patients' adherence to recommended treatment regimens. Poor adherence to multi-day regimens contributes to ongoing transmission and constitutes a risk factor for the selection and spread of specific drug resistance. The successful development of a single-dose antimalarial treatment regimen would allow for supervised administration by health care providers, potentially improving treatment outcomes in real-world settings. This would therefore constitute a major progress in the treatment of uncomplicated malaria in sub-Saharan Africa.

Artesunate-pyronaridine and sulfadoxine-pyrimethamine (SP) are marketed antimalarial drugs. While SP is administered as a single-dose therapy, it has suffered declining efficacy due to the development of resistant isolates. Still, it remains effective in the preventive treatment of malaria in pregnant women and is used on a large scale for this purpose in high transmission regions of Africa. Artesunate-pyronaridine is an ACT that is routinely administered over a three day period. However, it was shown that single dose treatment of asymptomatic malaria is possible. The combination of these two antimalarial drugs has therefore been proposed as a potential ad hoc combination for single dose therapy.

Preliminary phase II results of a novel single-dose combination of artesunate–pyronaridine–sulfadoxine–pyrimethamine (SPAP) show excellent efficacy and safety, with clinical phase II trials currently ongoing in adults and children in Gabon. However, key pharmacokinetic (PK) data are lacking. Understanding the PK profile of SPAP is crucial for rational dose selection, evaluating drug–drug interactions, and confirming safety across diverse populations. The evaluation of this single dose antimalarial treatment for its pharmacokinetic properties and its association with pharmacodynamics is therefore of high importance.

Hypothesis: A single-dose artesunate–pyronaridine–sulfadoxine–pyrimethamine (SPAP) regimen leads to high cure rates and is characterized by sufficient drug exposure in pharmacokinetic analysis. By understanding the PK profile dosing strategies may be optimized helping to bridge the efficacy–effectiveness gap, supporting adherence-independent malaria treatment, and potentially reducing transmission and resistance development.

Aims and Work Programme:

This work program will be performed by conducting a nested pharmacokinetic clinical trial in the treatment of uncomplicated malaria within the clinical phase II and III development program in Gabon and potentially other sub-Saharan African countries with high malaria transmission. The applicant is therefore expected to perform extended field-work in sub-Saharan Africa for the conduct of the clinical trials.

The PK analysis and the PK/PD modelling will be performed in collaboration with the Dept of Clinical Pharmacy at the University of Hamburg. The applicant is therefore expected to attend dedicated training courses in clinical pharmacology and pharmacokinetics and to collaborate closely with Prof Sebastian Wicha's group at the University of Hamburg.

1. **Classical rich pharmacokinetic evaluation:** a rich-PK study will be performed with intensive blood sampling for the assessment of drug concentrations. Non-compartmental analysis (NCA) for PK parameters, plasma protein binding assessment, and measurement of drug concentrations in specific compartments will be performed in collaboration with the Department of Clinical Pharmacy at the University of Hamburg (Prof Sebastian Wicha).
2. **Establishing a pharmacokinetic model for further population PK analysis:** based on the rich-PK analysis, a pharmacokinetic model will be established allowing for further population PK analysis of the drug combination. Population-PK analysis is important for the analysis of PK parameters in larger patient populations using sparse sampling strategies. PopulationPK analysis will allow a better understanding of potential co-variables influencing drug exposure and treatment outcomes and is therefore necessary for rational dosing strategies.
3. **Performance of a nested population PK study in clinical phase II and III development:** Sparse sampling strategies will be used to evaluate drug exposure, co-variables and specific patient populations. The sampling will be performed as nested study in the clinical phase II and III trials. The PK analysis and modelling will be performed in collaboration with the Department of Clinical Pharmacy at the University of Hamburg (Prof. Sebastian Wicha)
4. **Integrate PK/PD modeling and simulation:** PK-PD exposure-response modeling, probability of target attainment (PTA) simulations, covariate analysis on PK/PD parameters, and dose optimization simulations for vulnerable populations will be performed based on the available data from rich- and population-PK studies and established models

In Aim #1,#2, #3 a nested rich pharmacokinetic (PK) study will be conducted in adults and children at the Centre de Recherches Médicales de Lambaréné (CERMEL), Gabon, as part of a larger multicenter trial. Participants will receive the investigational single-dose SPAP regimen under rigorously controlled conditions. Blood sampling will capture absorption, distribution, and elimination phases to fully characterize concentration–time profiles. Drug quantification will use novel multiplex LC-MS/MS and HPLC-UV assays with advanced quality control. The resulting PK data will support:

- Non-compartmental analysis (NCA) to determine clearance, half-life, and volume of distribution.
- Establishing a robust PK model for the combination therapy for further population PK analysis.
- Performance of a nested population PK study using sparse sampling strategies
- Population PK modeling using nonlinear mixed-effects methods to describe variability and guide dose optimization across age, body weight, and nutritional status.

In Aim #4, pharmacodynamic (PD) endpoints will complement the PK assessment. Efficacy will be evaluated via parasitological monitoring (microscopy and PCR-adjusted cure rates at days 28 and 42). Safety monitoring will include adverse event reporting and routine lab tests (e.g., ALT/AST for hepatotoxicity). Resistance surveillance will focus on molecular markers (e.g., Pfk13, Pfdhfr, and Pfdhps mutations) to correlate with clinical drug efficacy. These PD assessments will anchor exposure–response relationships in clinically relevant outcomes and biological mechanisms. Integrated PK/PD analyses will connect exposure and outcome data. Multiple pharmacometric and physiologically based pharmacokinetic (PBPK) models will be compared for fit, predictive accuracy, and usefulness in guiding dosing strategies. Specific approaches include:

- PK-PD exposure–response modeling linking drug exposure to efficacy.
- Probability of target attainment (PTA) simulations estimating the likelihood of achieving parasitological endpoints at relevant MICs.
- Covariate analyses examining effects of demographic, host-, and parasite-factors.
- Dose optimization simulations tailored for vulnerable groups like children and pregnant women.

Project-related publications: (max. 5)

1. Ekoka Mbassi D, Pfaffendorf C, Mombo-Ngoma G, Kreuels B, Ramharter M. Real-life effectiveness of anti-malarial treatment regimens: what are we aiming for? Malar J. 2023;22(1):189.
2. Making the most of existing antimalarial medicines: a single dose cure with sulfadoxine-pyrimethamine plus artesunate-pyronaridine. Mombo-Ngoma G, Ramharter M, Zoleko Manego R, Lell B, Bassat Q, Aide P, Maiga Ascofare O, Wells TNC, Djimde A, Ntoumi F, Kremsner PG. Malar J. 2025 Sep 30;24(1):300.
3. Pfaffendorf C, Mischlinger J, Dejon-Agobé JC, et al. Multiplex LC-MS/MS assay for simultaneous quantification of artesunate and its active metabolite dihydroartemisinin with pyronaridine, proguanil, cycloguanil, and clindamycin in pharmacokinetic studies. Malar J. 2025;24(1):168. Published 2025 May 27. doi:10.1186/s12936-025-05387-6
4. Safety and efficacy of pyronaridine-artesunate paediatric granules in the treatment of uncomplicated malaria in children: insights from randomized clinical trials and a real-world study. Ramharter M, Djimde AA, Borghini-Fuhrer I, Miller R, Shin J, Aspinall A, Richardson N, Wibberg M, Fleckenstein L, Arbe-Barnes S, Duparc S. Malar J. 2024 Feb 28;23(1):61.
5. Pyronaridine-artesunate real-world safety, tolerability, and effectiveness in malaria patients in 5 African countries: A single-arm, open-label, cohort event monitoring study. Tona Lutete G, Mombo-Ngoma G, Assi SB, Bigoga JD, Koukouikila-Koussounda F, Ntamabyaliro NY, Ntoumi F, Agnandji ST, Groger M, Shin J, Borghini-Fuhrer I, Arbe-Barnes S, Allen SJ, Kremsner PG, Miller R, Duparc S, Ramharter M; CANTAM study group. PLoS Med. 2021 Jun 15;18(6):e1003669.

Graphical Abstract