

Population Pharmacokinetics and Dose Optimization of a Novel Triple Combination Therapy: Arterolane-Piperaquine-Mefloquine in Kenyan Children with Malaria

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Background

Resistance to artemisinin derivatives and partner drugs has been reported in the South-East Asia region. Thus, novel antimalarial drug combinations are needed. One new treatment is the fixed-dose combination of arterolane and piperaquine, which has been developed to treat uncomplicated *P. falciparum* malaria. Understanding pharmacokinetic properties of novel drug is essential for rational dose optimisation and selection.

Objectives

- To characterize the population pharmacokinetic properties of arterolane and piperaquine when administered with and without mefloquine in Kenyan children.
- Evaluate the relationship between drug exposure and QT interval prolongation.
- Develop and explore a weight-based dosing strategy.

Methods

Design: Open-label clinical study involving 145 children (age 2–12 years) with uncomplicated *P. falciparum* malaria.

Weight-based dosing, administered at 0, 24, and 48 hours was designed to achieve an arterolane dose of 4 mg/kg, a piperaquine dose of 20 mg/kg and a mefloquine dose of 8 mg/kg of body weight. This approach aligns with the WHO's recommended dosing guidelines.

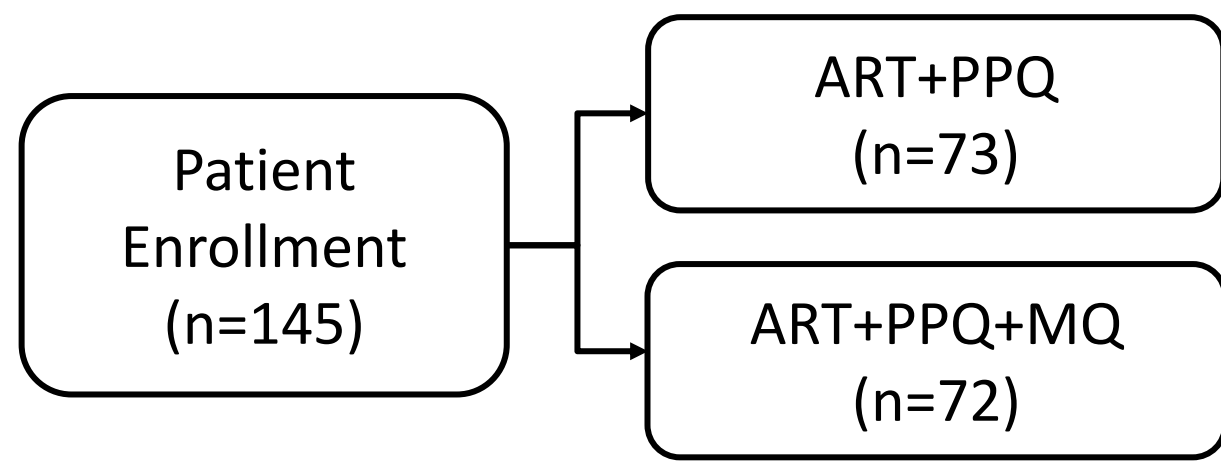


Figure 1. Patient flow diagram for PK/PD analysis; ART=Arterolane, PPQ=Piperaquine, MQ=Mefloquine

Blood sampling were obtained Pre-dose, 0.5, 2, 6, 18, and 48 after baseline in half the patients and 1, 3, 12, 24, and 72 hours after baseline in the other half of patients.

Nonlinear mixed effect modelling (NONMEM) was performed to characterise the pharmacokinetic properties of arterolane piperaquine and mefloquine.

Model-based simulations: Simulations assessed exposures under current dosing across body weights (5–100 kg)

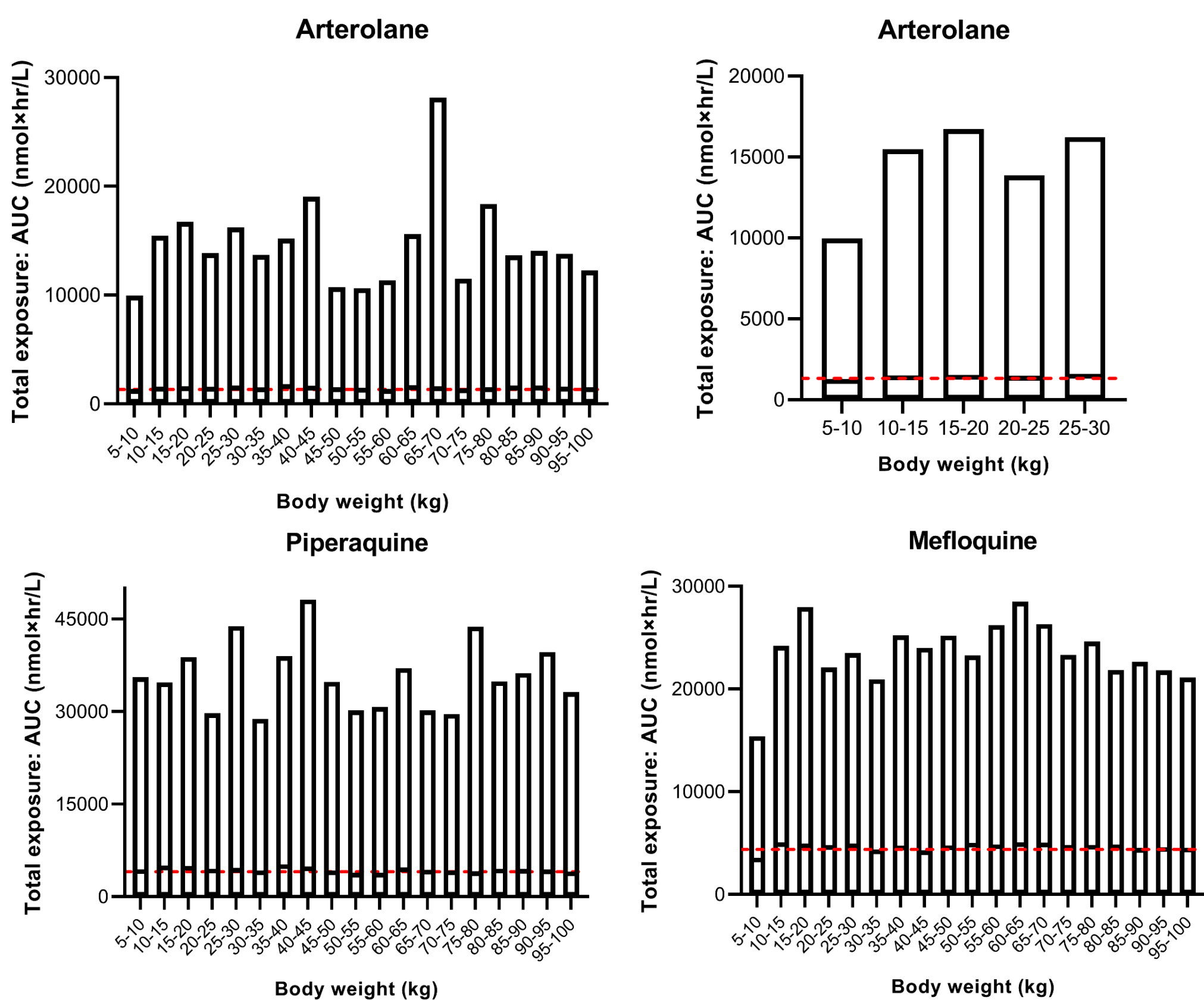


Figure 2. Simulated Total exposure (AUC) of arterolane, piperaquine and mefloquine across body weight bands following standard ACT-dosing and investigational dose in this study. Each bar represents the distribution of simulated exposures within a 6-kg weight band. Dashed red lines are the mean exposures in a typical patient at 60 kg, receiving standard dosing.

Conclusions

- Successfully characterized the pharmacokinetic properties of arterolane, piperaquine and mefloquine in Kenyan children.
- no increase in drug-associated QT prolongation in the triple combination therapy, supporting the safety of this combination.
- Model-based simulations revealed that standard dosing may lead to subtherapeutic exposures in smaller children, highlighting the need for refined dosing strategies.

Pharmacokinetics

- Arterolane:** 1-compartment with 2-transit absorption.
- Vomiting influenced bioavailability (F)** — modelled using Emax as a function of time to vomit following each dose ($T_{\text{vomit}} = 1-12$ hours)
- Mefloquine:** 2-compartment with 2-transit absorption, carboxymefloquine can be described by 1-compartment disposition. Body weight was implemented as allometric function on all clearance and volume of distribution parameters.

- QTc Safety:**
- No notable difference in QTc prolongation between 2 groups.
- Simulations:**
- Younger children (<10 kg) had lower drug exposures compared to older children and adults under current WHO dosing.
 - Findings suggest current dosing may be insufficient for smaller children.

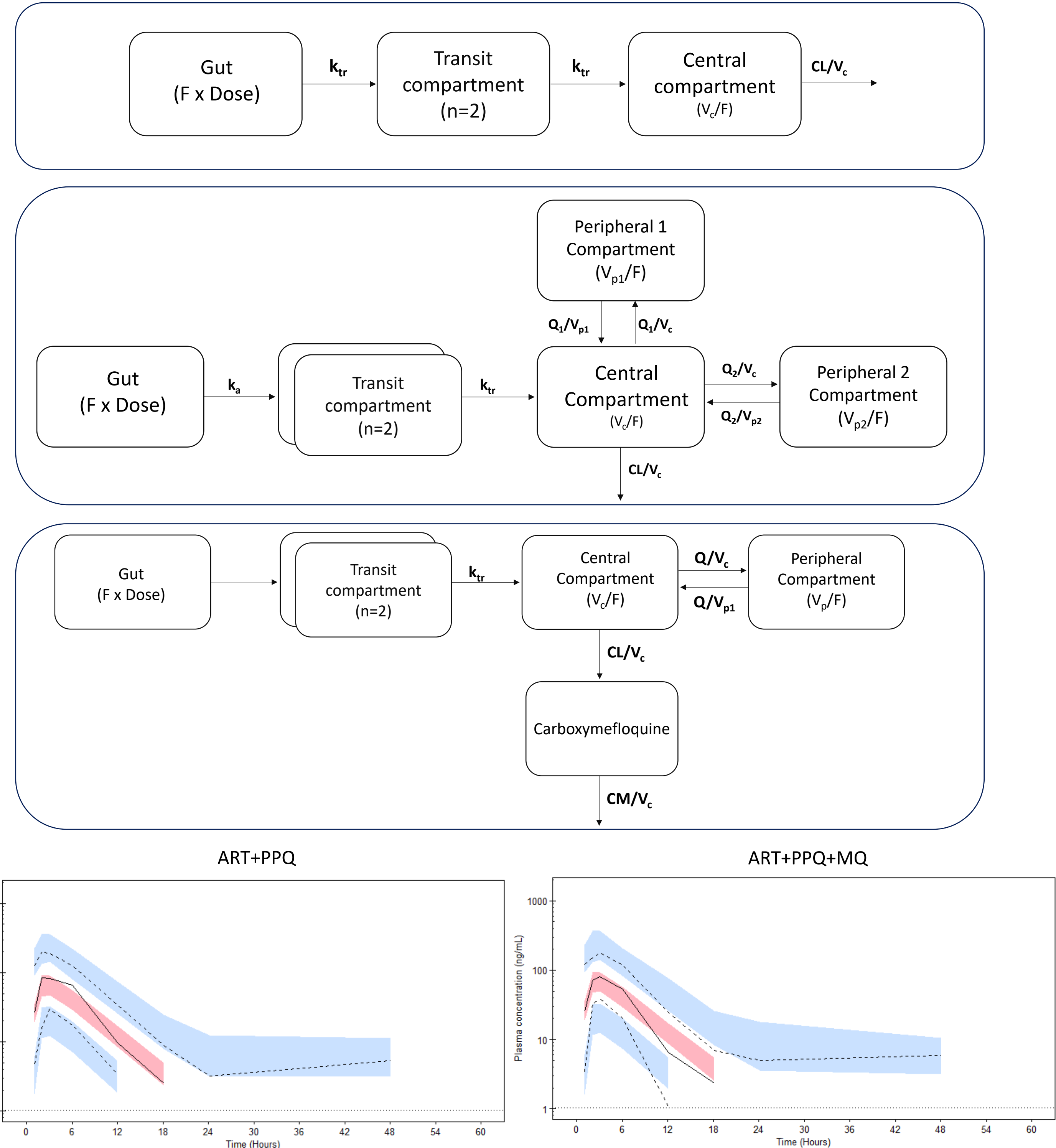


Figure 3. Structural model of arterolane, piperaquine and mefloquine and the visual predictive check (VPC) of the final population pharmacokinetic model of arterolane-piperaquine co-administered with mefloquine.

Reference: See the online abstract

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