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Introduction

- Atovaquone (ATQ) is a highly water insoluble antimalarial drug, which exhibits a long half-life due to the absence of metabolic clearance.
- ATQ is given orally in combination with proguanil for treatment but monotherapy has been shown to be effective for chemoprophylaxis in challenge studies.
- Adherence negatively impacts efficacy for ATQ.¹
- A long-acting injectable (LAI) formulation of ATQ is in development that provides protection from *Plasmodium berghei* sporozoites for 28 days after intramuscular (IM) administration to mice.¹
- The aim of this study was to use PBPK modelling to estimate dose and release rate parameters which provide adequate ATQ exposure for 28 days in humans after LAI administration.

Methods

- A previously published whole-body PBPK model² with an IM compartment describing first-order drug release kinetics from the administration site in Simbiology (MATLAB 2018a) was used for ATQ model simulations; the drug specific parameters are shown in Table 1.
- Simulations were performed in one hundred virtual healthy individuals (50% women, 18-60 years, 77 ± 19 kg (range, 40-120 kg)).³
- The model was initially qualified against available data for a single 750 mg oral dose of ATQ oral formulation.⁴
- Model qualification was assumed if the mean simulated values i.e. AUC, C_{max} and plasma concentration time curve were within ± 50% from the mean observed values.
- Target concentrations were defined as 1.83 mg/L⁵ and 0.2 mg/L⁶ for treatment and prophylaxis, respectively.

Table 1 Drug specific parameters used in the PBPK model

	Atovaquone
Log P	75.8
pKa	8.23 (acid)
Blood-to-plasma ratio	91.248
Protein binding	799.9%
Polar surface area	854.37
Hydrogen bond donors	81
CL/F (L/h)	1030.4 ± 7.3

Results

- The ATQ model was successfully qualified against observed data⁴ with simulations within ± 50% from the mean observed values (Figure 1 & Table 2).
- The PBPK model was assessed for doses every 4 weeks between 1000 – 2000 mg and 100 – 250 mg for treatment and prophylaxis, respectively; release rate constants from 5×10^{-4} – 3×10^{-3} h⁻¹ were simulated (Figure 2a & 2b).
- For treatment, a minimum dose of 1500 mg with release rate constants between 1.5×10^{-3} – 2.5×10^{-3} h⁻¹ were predicted for monthly administration (Figure 3a).
- For prophylaxis, a minimum dose of 200 mg between the release rate constants of 1×10^{-3} – 3×10^{-3} h⁻¹ were predicted for monthly administration (Figure 3b).

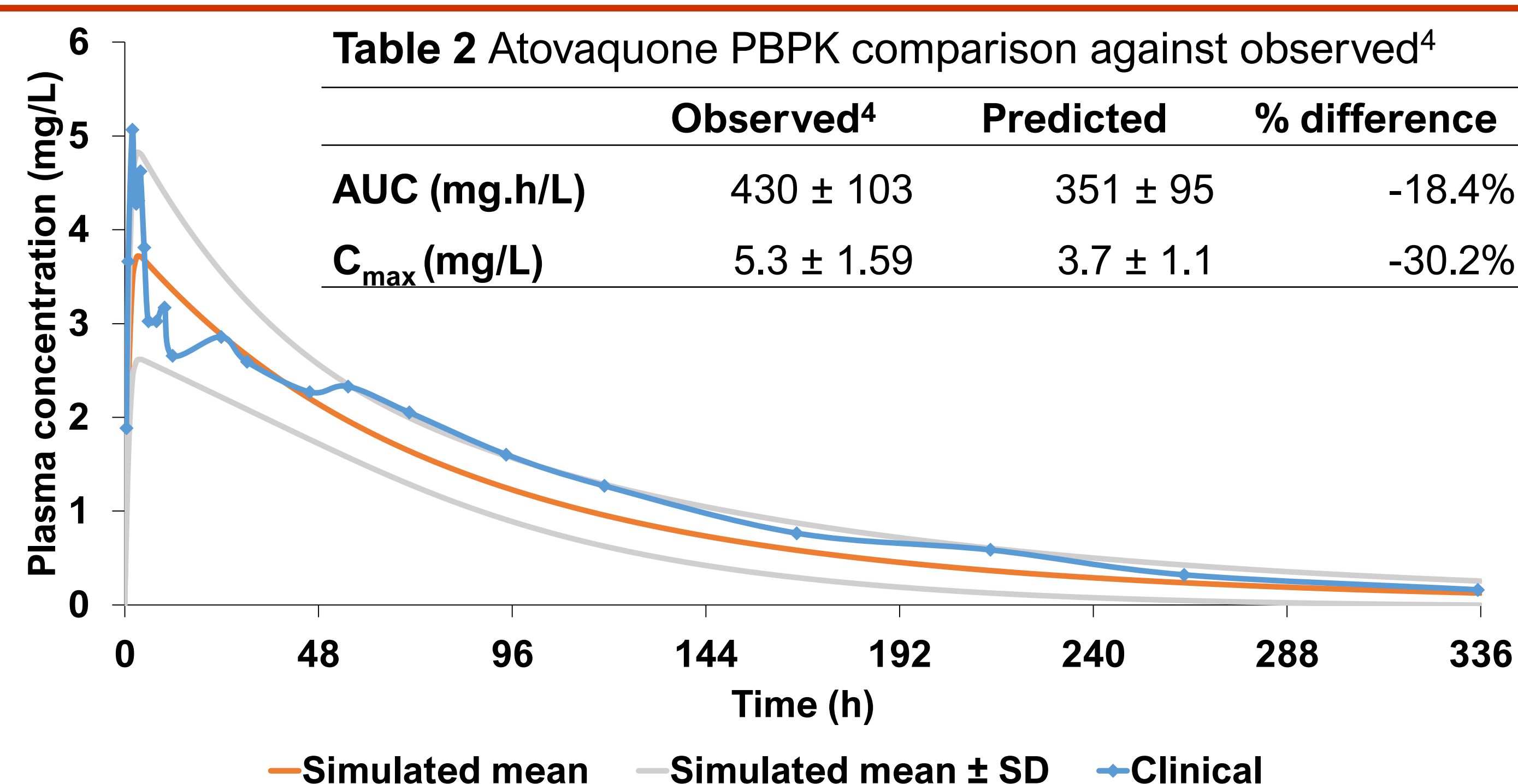


Figure 1 Atovaquone model qualification against observed data for a single 750 mg oral dose.

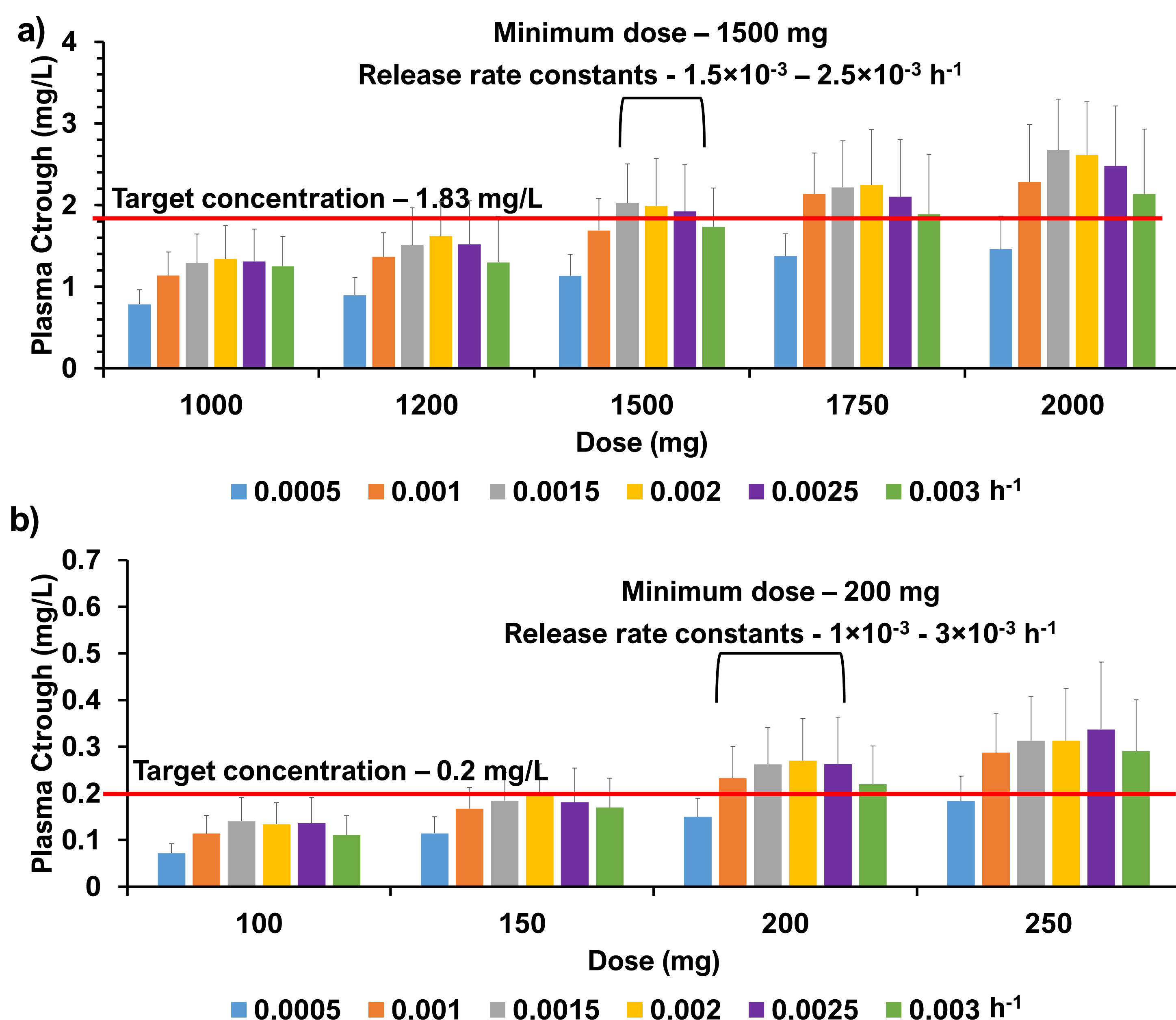


Figure 2 Plasma C_{trough} of intramuscular atovaquone every 4 weeks at various doses and release rates a) for treatment, b) for prophylaxis.

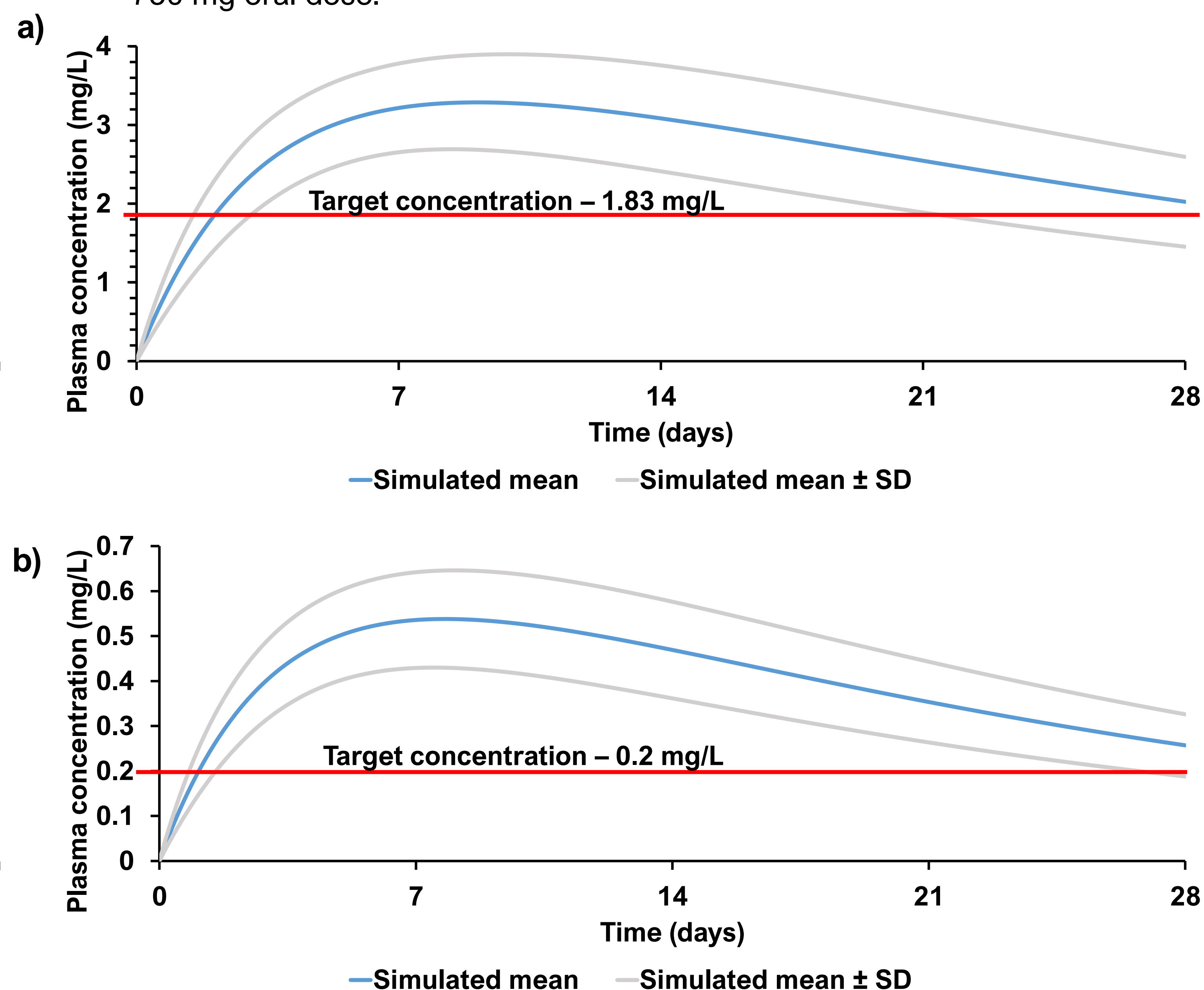


Figure 3 Plasma concentration of intramuscular atovaquone a) For treatment, 1500 mg at 1.5×10^{-3} h⁻¹ b) For prophylaxis, 200 mg at 2×10^{-3} h⁻¹.

Conclusions

- These simulations strongly support the applicability of a monthly administration of ATQ LAI for therapy and chemoprophylaxis, and longer durations may be possible with higher doses for the latter.
- LAI suspensions containing 300 mg/ml ATQ have now been developed, which bring monthly self-administration within scope for chemoprophylaxis providing similar exposures can be achieved after sub-cutaneous dosing.⁶
- For therapy, the current absence of a proguanil LAI formulation will limit enthusiasm for the approach.

References

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