

Model-informed trial design for the malaria transmission blocking antibody TB31F

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Introduction

- TB31F is a novel malaria transmission-reducing monoclonal antibody.¹
- Tolerated well and reduced the malaria transmission over 84 days in healthy volunteers.²
- TB31F-Mali study aims to:
 - Determine tolerability and efficacy of TB31F in the target population: naturally infected Malian children (aged 10-18).
 - Determine the exposure-response (EC50) in the target population.
- Malaria transmission reduction is determined by direct skin feeding (DSF).
 - Very burdensome procedure.
- Unknown what dose to administer and what time to perform the DSF to get best estimate of the EC50.

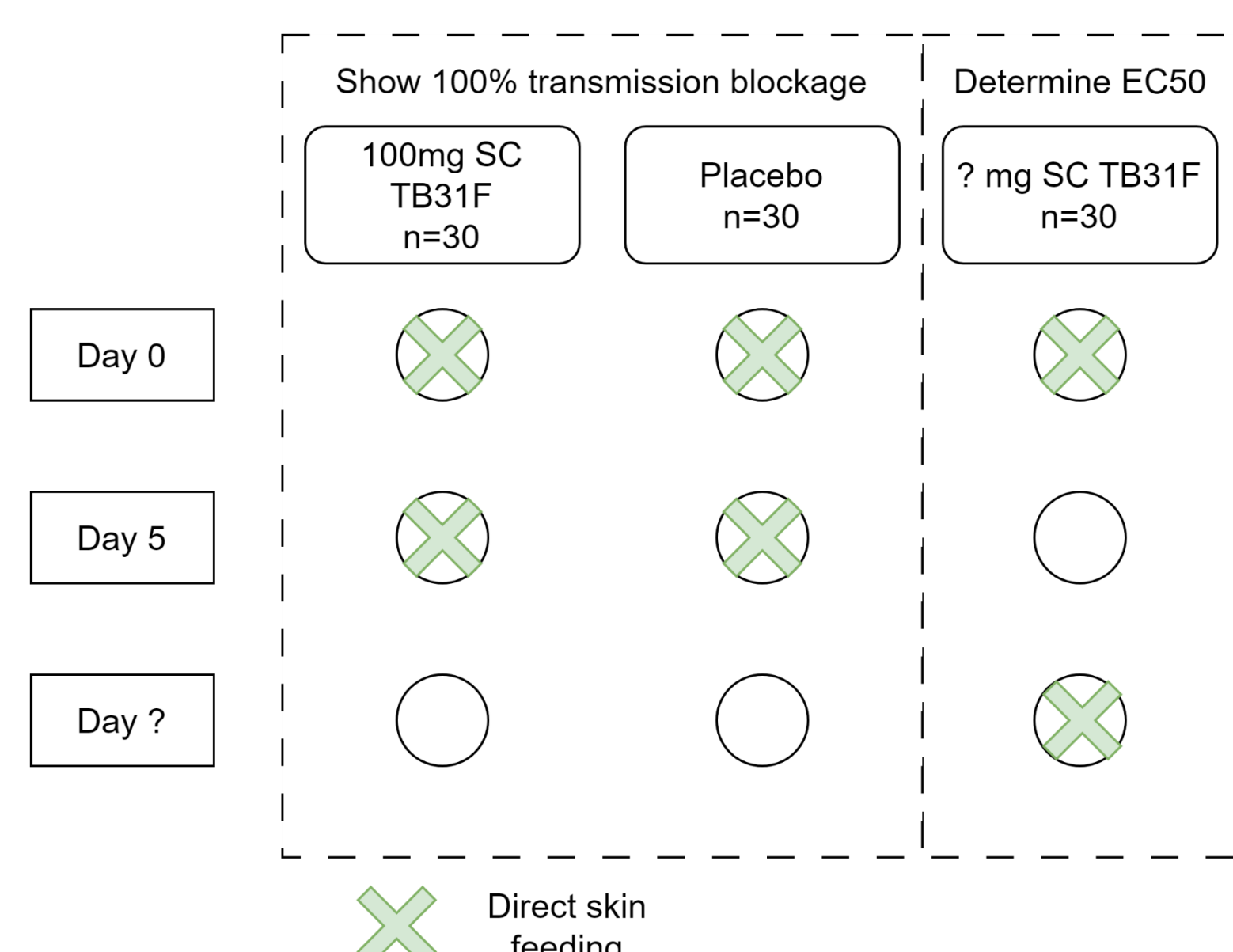


Figure 1: Proposed clinical trial design for the TB31F-Mali study.

Objective: Use model informed clinical trial design to inform the TB31F-Mali study.

- Determine the optimal dose to determine the EC50.
- Determine optimal DSF timepoint to determine the EC50.
- Reduce clinical trial burden.

Methods

- Clinical trial simulations were performed using a published pharmacokinetic-pharmacodynamic model.³

Determination of optimal dose to inform the EC50

- TB31F exposure simulated following 100mg, 50mg, and 30mg SC TB31F.
- Large African children population (n=10000).⁴
- EC50 derived in healthy volunteers (2.18 mg/L) was used as target exposure.
 - Suggested to have most power of determining the EC50.

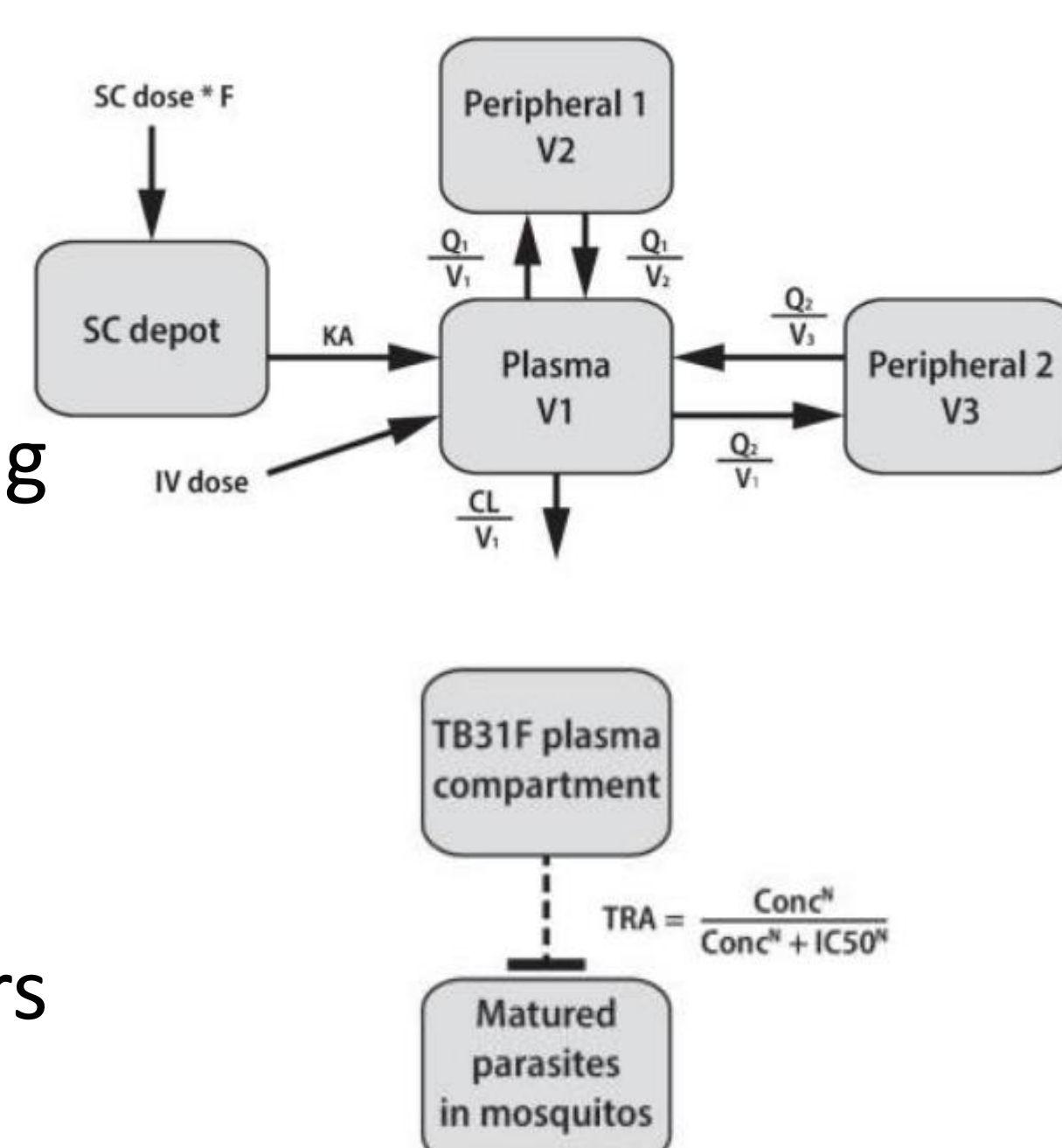


Figure 2: Pharmacokinetic-pharmacodynamic model used for clinical trial simulations

Determine optimal DSF timepoint to inform the EC50

- Clinical trials were simulated following the proposed design in figure 1.
- DSF was simulated for the EC50 arm at baseline and at days 1,2,3, or 5.
- The EC50 bias and precision was determined in n=1000 clinical trials for each of the trial designs using stochastic simulation and estimation (SSE) procedure.⁵
- Parameter uncertainty of the IC50 was incorporated in the SSE procedure.

Results

Determination of optimal dose to inform the EC50

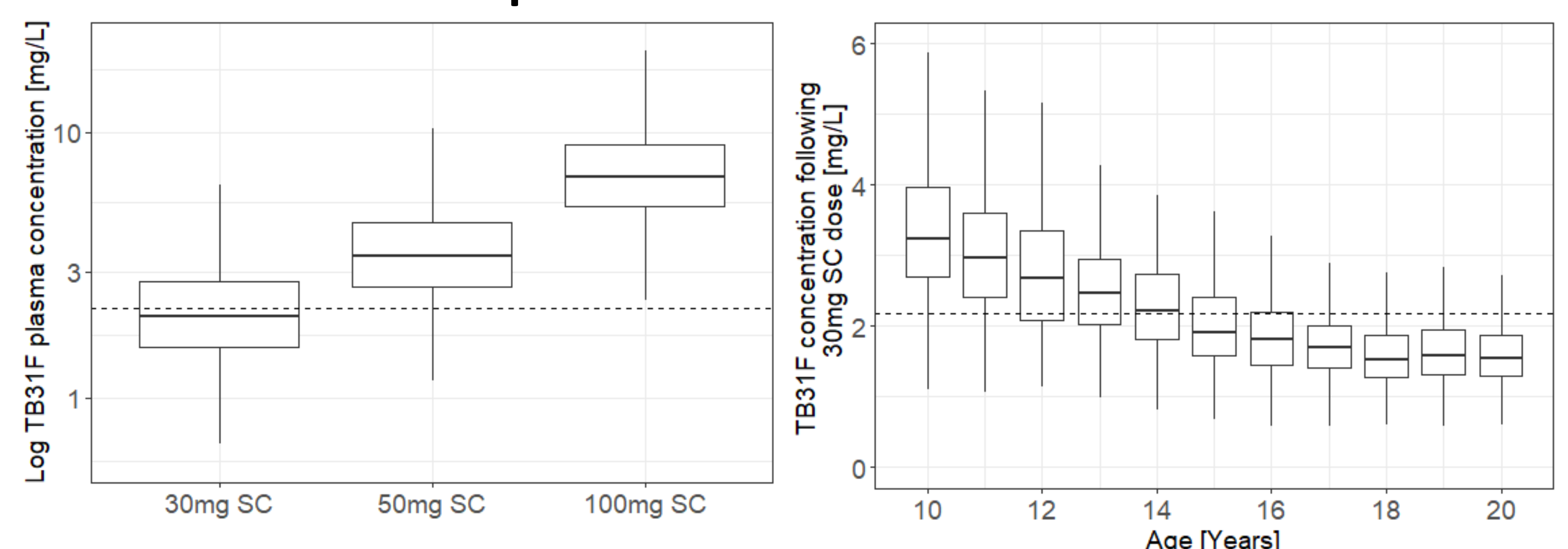


Figure 3 (left): Predicted concentrations following a 100mg, 50mg, or 30mg SC dose at day 1. Figure 3 (right): Predicted concentrations following a 30mg SC dose at day 1, stratified per age group. The dotted lines represent the EC50 (2.18mg/L) derived in healthy volunteers.

- The 30mg SC dose was selected to determine the EC50

Determine optimal DSF timepoint to inform the EC50

DSF timepoints for the 30mg SC arm	Bias (mg/L)	Precision (RMSE%)
Day 0 + day 1	-0.176	10.4
Day 0 + day 2	-0.00278	10.7
Day 0 + day 3	-0.0299	15.2
Day 0 + day 5	-0.0312	17.8

- Day 1 was selected to perform the DSF in the EC50 determination arm, because of low bias, good precision, and ease of implementation.

Conclusion and discussion

- A 30mg SC dose of TB31F is expected to result in concentrations close to the EC50 determined in healthy volunteers.
- DSF assays provided the most information on estimating the EC50 when performed at day 1 following a 30mg SC dose.
- The clinical trial burden was reduced by only having two DSF assays per participant.

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