

Evaluation of efficacy predictors and probability of pharmacological success for a novel compound to treat parasitic disease proposed for first-time-into-human

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Background

- Parasitic diseases represent a global health burden.
- A novel compound appeared highly efficacious against a parasitic disease in both in vitro and in vivo animal studies.
- The probability of pharmacological success (PoPS) is the probability of achieving desired pharmacological and safety response rates in a treated population.
- PoPS supports progression decisions at any stage and was here applied prior to first-in-human*.

*Here modified data are presented to maintain the blinding.

Methods

Pharmacokinetics:

- Human PK projections for oral BID dosing were based on non-clinical data and accounted for inter-subject variability and body weight.

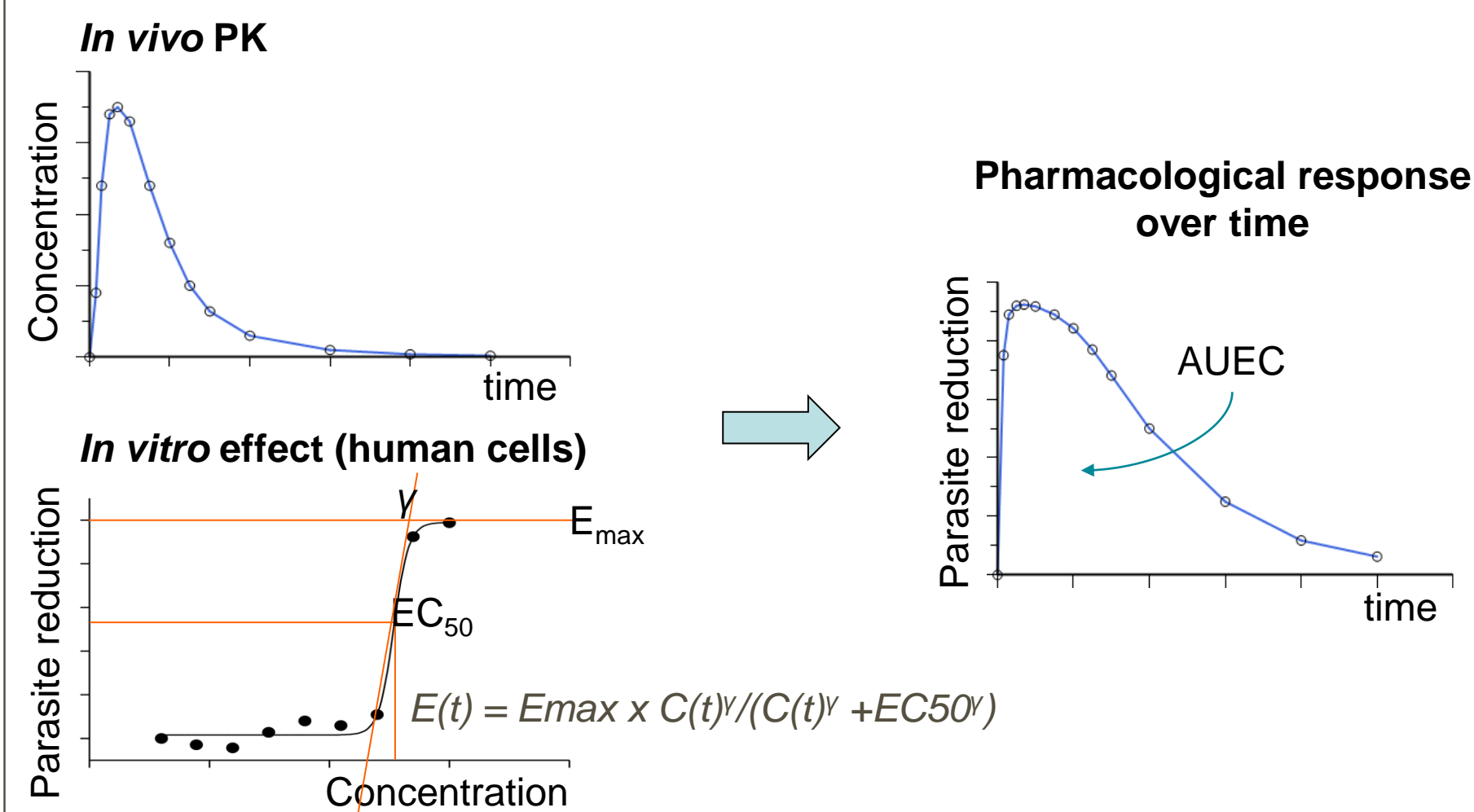
Efficacy:

- In a preclinical model, indices evaluated both based on total blood and free plasma were: AUC_{24h} , $time > EC50_{24h}$, $time > EC90_{24h}$, and area under the effect curve $E(t)$ over 24 hours ($AUEC_{24h}$, see Figure 1).
- In vivo effect vs index data were fitted. The best index was identified based on highest R^2 and selected as efficacy driver.
- The value of efficacy driver providing 95% of parasite reduction (from standard of care) was derived.

PoPS:

- Uncertainty on $EC50$ and γ (Hill slope, see Figure 1) was included.
- Success criterion was: 95% of subjects with safe exposure, and 80% (for compound used as monotherapy) or 60% of subjects (for compound used in combination) with efficacy (i.e., 95% of parasite reduction).

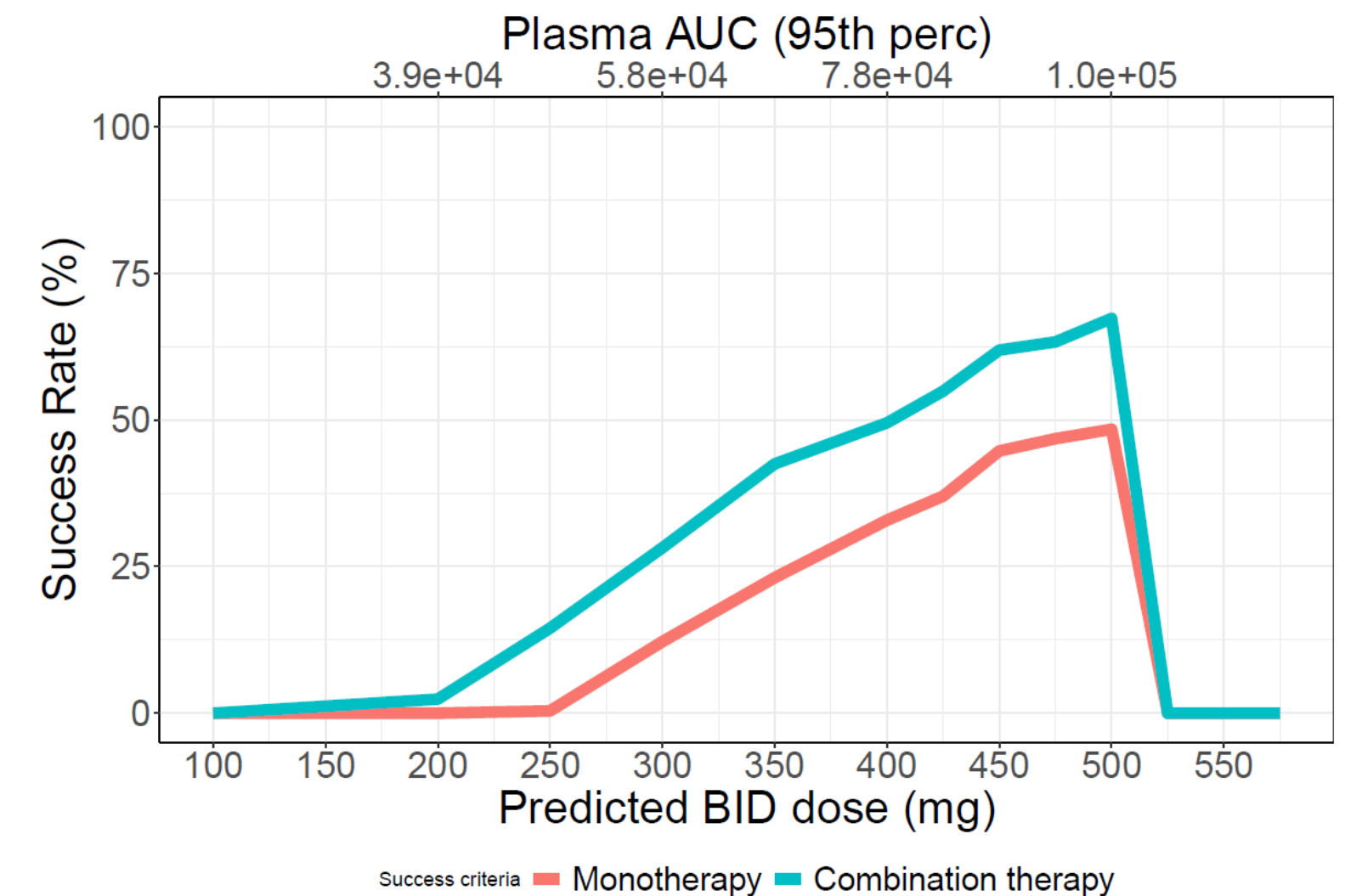
Figure 1. Effect curve and $AUEC_{24h}$ derivation.



Results

- The best indices were $time > EC50_{24h}$ and $AUEC_{24h}$ based on total blood. $AUEC_{24h}$ was selected as the driver for efficacy.
- For monotherapy and combination therapy, PoPS reached 48.4% and 67.3%, respectively, at 500 mg BID (Figure 2).

Figure 2. PoPS for candidate compound used as monotherapy or in combination.



Conclusions

- $AUEC_{24h}$ is a newly proposed PK-PD index. $AUEC_{24h}$ represents a time-integrated pharmacodynamic response. It considers the whole drug concentration profile capturing its shape in terms of collective pharmacology (better translatable across species).
- Computation of the compound-specific PoPS, allowed to quantify the impact of uncertainty on success and gave more confidence in proceeding with the FIH trial.
- Update of PoPS when new information is gathered (e.g. about the actual PK profile in human) allows to support progression decisions at future phases of development.