ASCPT

FROM MOLECULE TO PATIENT

ASCPT 2019 ANNUAL MEETING

Retrospective Analysis Using Pharmacokinetic/ Pharmacodynamic Modeling and Simulation Offers Improvements in Efficiency in the Design of Volunteer Infection Studies for Antimalarial Drug Development

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**Employee of Cognigen Corporation at the time this work was performed.*

Antimalarial Drug Development

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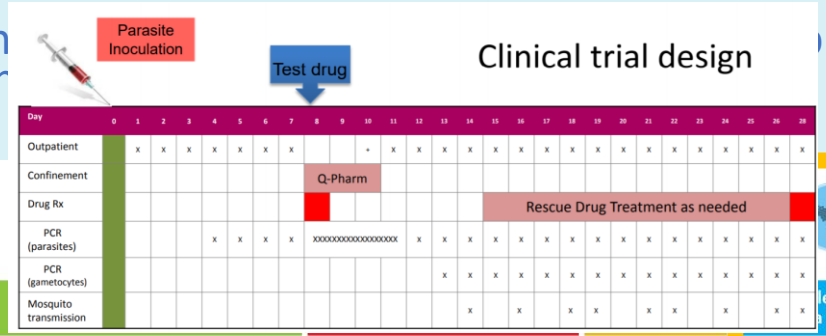
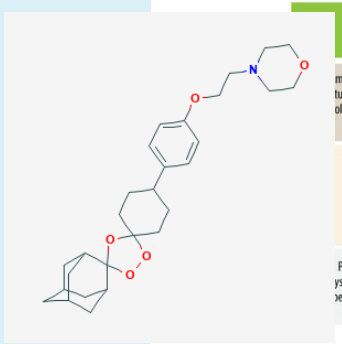
- 2018 World Malaria Report shows stall in progress towards eradication
- Curren… remain… …urden

Strengthened Use of Data



New Drugs

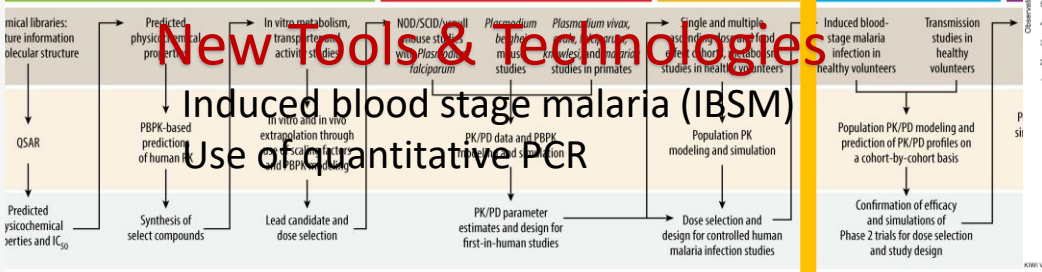


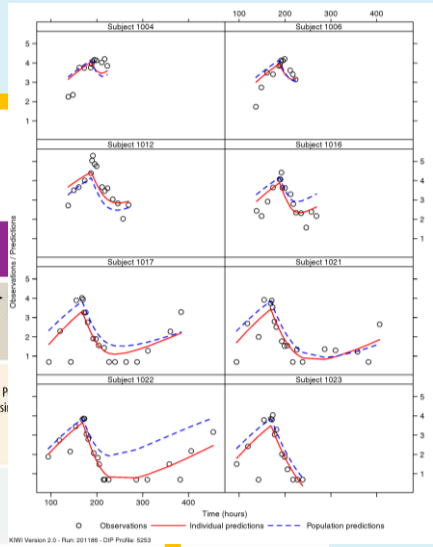
artefenomel

New Tools & Technologies

Induced blood stage malaria (IBSM)

Use of quantitative PCR





Integrated clinical trial design with PK/PD modeling and simulation

McCarthy JMa. Public Workshop: Clinical Trial Design Considerations for Malaria Drug Development In: Services HaH, editor. White Oak, Maryland: FDA; 2016. pp. 1-52.

Proof-of-Concept Multi-Dose Cohort

Goal: *Investigate if an alternate design with a multiple-dose-level single cohort, paired with PK/PD modeling and simulation could offer improvements in efficiency of the design of VIS for antimalarial drug development.*

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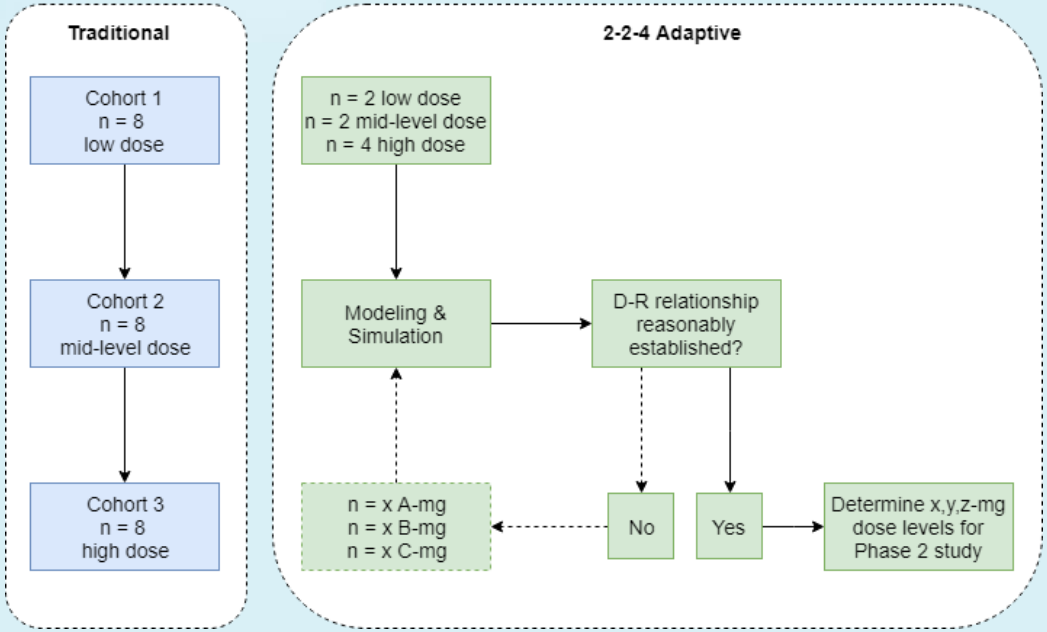
VIS Study Design



Objectives

- Generate multi-dose initial cohort
- Develop PK/PD model for initial cohort
- Simulate range of doses in Phase 2 trial from PK/PD model
- Compare simulations to observed Phase 2 trial data

Methods

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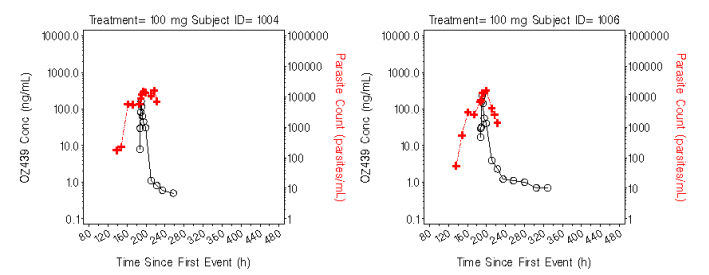
Pharmacokinetic Model

- 2- and 3-compartment models were tested
- PK and PD were modeled sequentially

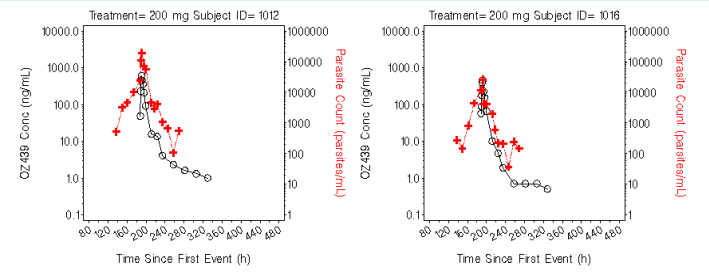
Pharmacodynamic Model

- Parasite growth and net parasite growth were evaluated with linear, logistic, and Gompertz-type functions
- Drug effect was evaluated with maximum pharmacologic effect (E_{max}) model, as well as with E_{max} model with an indirect response component

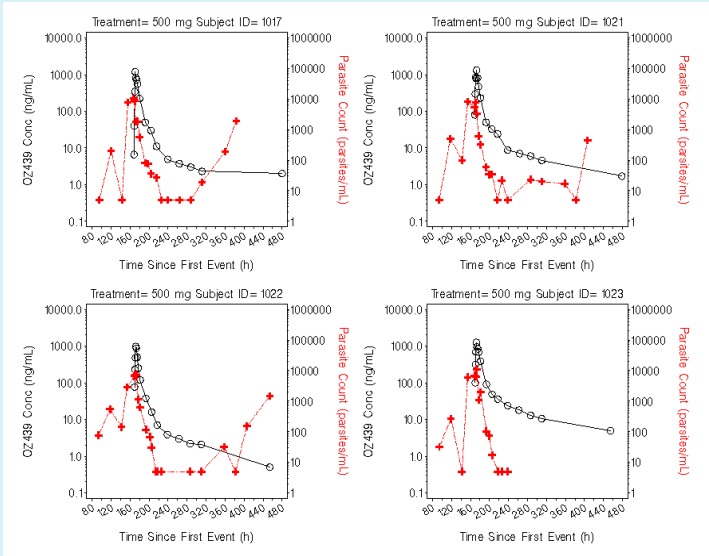
100 mg



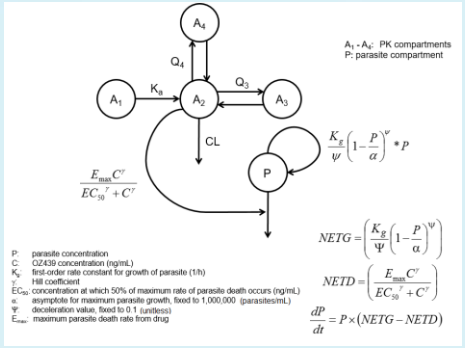
200 mg



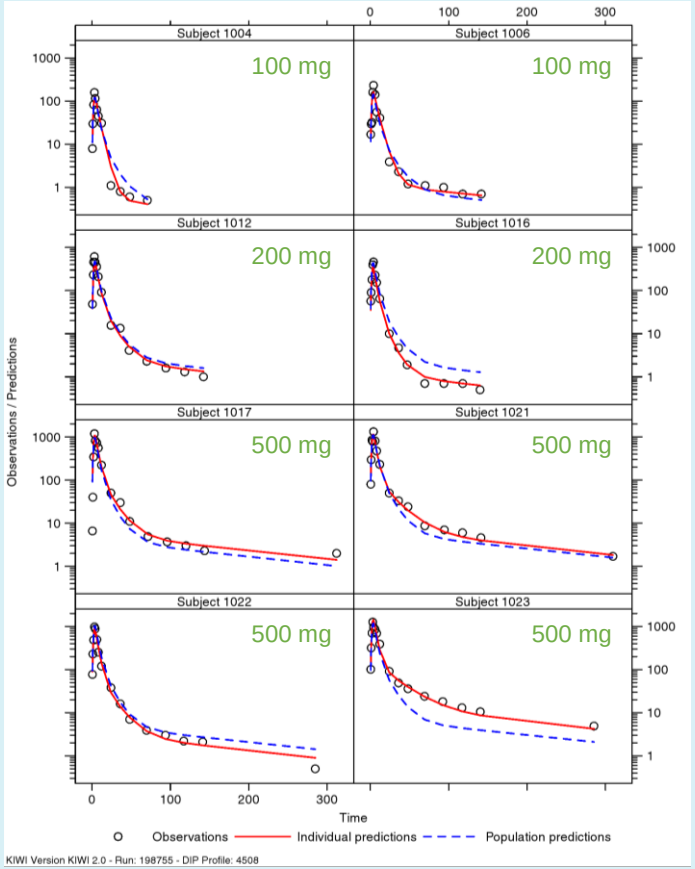
500 mg

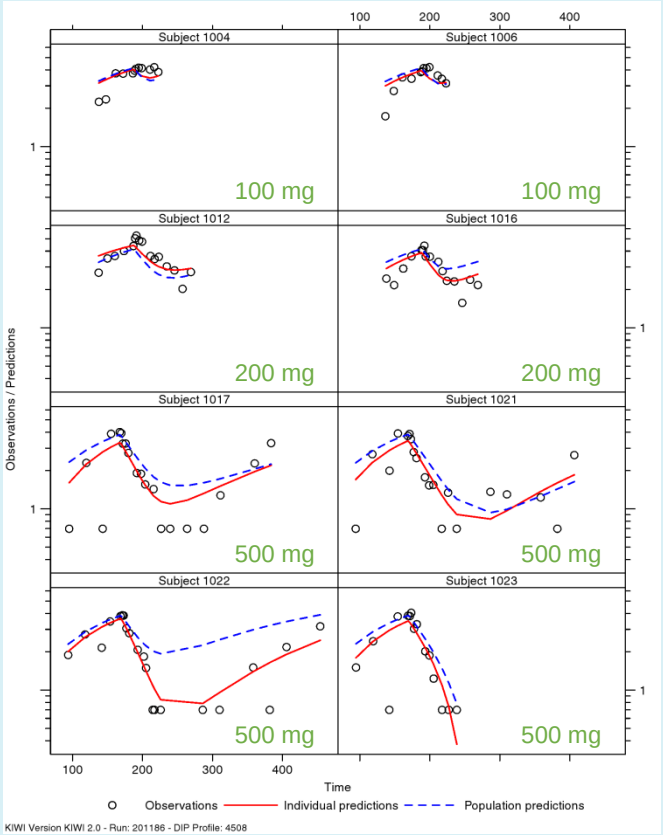


Results: 2-2-4 PK/PD Model



PK/PD Model





Methods:
Simulation of Phase 2a Trial

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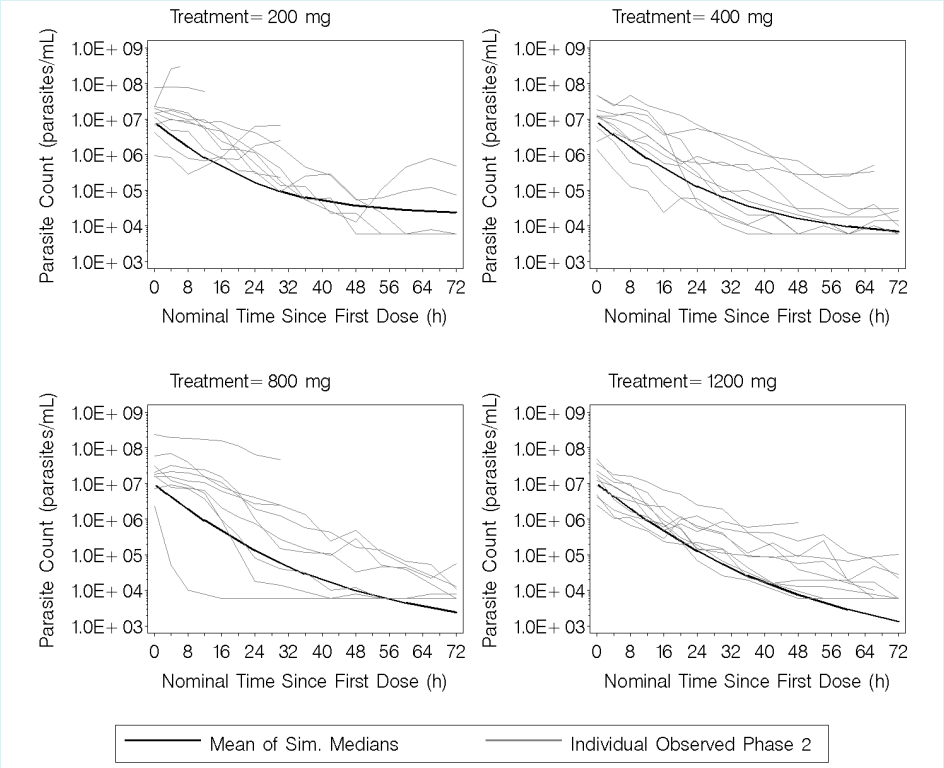
- 500 replicates of IBSM study with single dose cohorts (for example, 200, 400, 800, and 1200 mg) with 8 patients per cohort
  - Body weight values were simulated based on body weight distribution from full IBSM study
  - Unique baseline parasite was assigned to each patient ID by randomly selecting from distribution of baseline parasite counts from two phase 2 trials
- Cure versus recrudescence
  - Simulated data were censored where if a patient's individual predicted parasite count was ≤ 0.003 parasites/mL, patient was considered to be "cured"
  - If patients were not cured, they were considered to have "recrudesced"

Study Type	Cohort Information	Drug Dosing	Parasite Information	Rescue Medication
Phase 2	Cohort 1: n = 10 Cohort 2: n =10 Cohort 3: n = 9 Cohort 4: n = 11 Total: 40* *Patients who presented with *Plasmodium vivax* malaria were excluded from the comparison	Cohort 1: 800 mg Cohort 2: 400 mg Cohort 3: 200 mg Cohort 4: 1200 mg (all oral suspension in fed condition)	Patients presented with symptomatic malaria and 5,000 to 50,000 parasites/uL (*Plasmodium falciparum*) - detected with microscopy LLOQ ~10,000 to 100,000 parasites/mL	Definitive treatment given after 72 hours postdose of artefenomel, or earlier if deemed clinically necessary

Results:
Simulation of Phase 2a Trial

- 2-2-4 design allowed for characterization of dose-response relationship after administering drug to only 8 patients in 1 cohort
- Inclusion of 3 doses in first cohort allows for early estimation of key PD parameters (for example, E_{max} and EC_{50}) using data with wider dynamic range, which would typically be impossible from 1 dose cohort in typical IBSM study



Conclusions and Prospectus, v2

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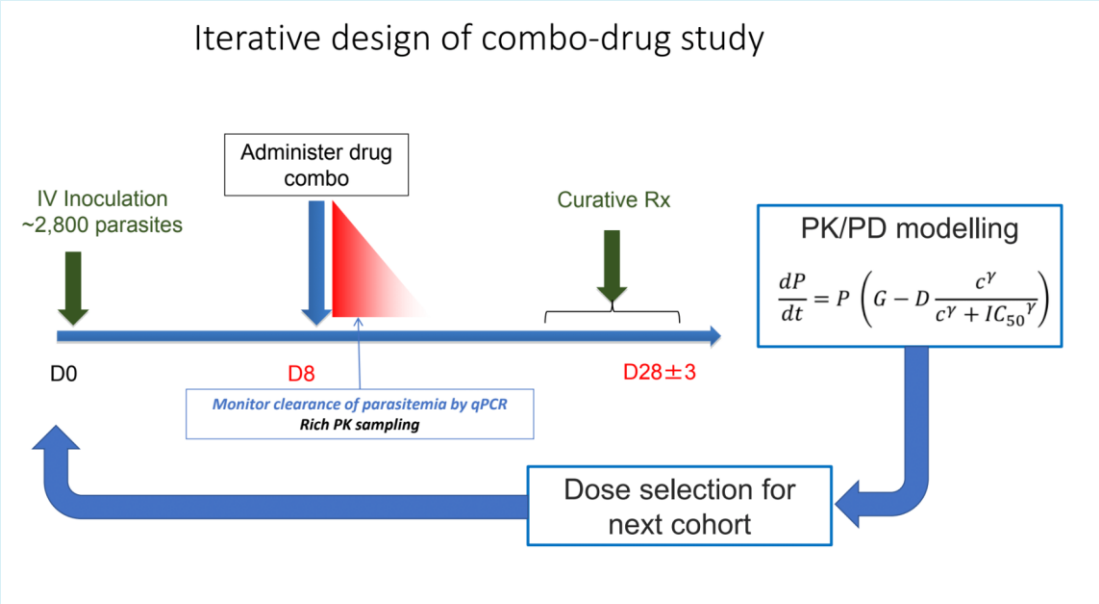
- Impact
  - Work is part of larger effort to integrate modeling and simulation into iterative study designs
- Future / Ongoing Work
  - Statistical powering of future cohorts
  - Parameter identifiability
  - Repeat with second drug
  - Multiple stochastic random draws of “initial cohort”



Slide courtesy of Dr. James McCarthy’s presentation, “Accelerating clinical development of antimalarials,” ASTMH 2018.

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