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

- 2018 World Malaria Report shows stall in progress towards eradication
- Current tools save millions of lives, but disease burden remains high

New Drugs
- artefenomel

New Tools & Technologies
- Parasite Inoculation
- Clinical trial design
-Transfusion studies in healthy volunteers
- Induced blood stage malaria infection in healthy volunteers
- PK/PD parameter estimates and design for Phase 2 trials for dose selection and study design
- Use of quantitative PCR

Strengthened Use of Data

Integrated clinical trial design with PK/PD modeling and simulation
**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.

**Proof-of-Concept Multi-Dose Cohort**

**VIS Study Design**

**Traditional**
- Cohort 1
  - n = 8
  - low dose
- Cohort 2
  - n = 8
  - mid-level dose
- Cohort 3
  - n = 8
  - high dose

**2-2-4 Adaptive**
- n = 2 low dose
- n = 2 mid-level dose
- n = 4 high dose

**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: 2-2-4 PK/PD Model

**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 ($E_{\text{max}}$) model, as well as with $E_{\text{max}}$ model with an indirect response component
Results: 2-2-4 PK/PD Model
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”

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Cohort Information</th>
<th>Drug Dosing</th>
<th>Parasite Information</th>
<th>Rescue Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>Cohort 1: n = 10</td>
<td>Cohort 1: 800 mg</td>
<td>Patients presented with symptomatic malaria and 5,000 to 50,000 parasites/uL (<em>Plasmodium falciparum</em>) - detected with microscopy LLOQ ~10,000 to 100,000 parasites/mL</td>
<td>Definitive treatment given after 72 hours postdose of artefenomel, or earlier if deemed clinically necessary</td>
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<tr>
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<td>Cohort 2: n = 10</td>
<td>Cohort 2: 400 mg</td>
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<td></td>
<td>Cohort 3: n = 9</td>
<td>Cohort 3: 200 mg</td>
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<td>Cohort 4: n = 11</td>
<td>Cohort 4: 1200 mg (all oral suspension in fed condition)</td>
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<td></td>
<td>Total: 40*</td>
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*Patients who presented with *Plasmodium vivax* malaria were excluded from the comparison
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, $E_{\text{max}}$ and $E_{\text{C50}}$) using data with wider dynamic range, which would typically be impossible from 1 dose cohort in typical IBSM study
Conclusions and Prospectus

• 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”

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