Model-informed Malaria Drug Development from Animal Models to Phase II

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Outline

• Plan for the development of antimalarial treatment and the role of Modeling & Simulation

• Translation of the PKPD relationship across the pharmacological models (mice, challenge volunteers, patients): one example

• Conclusion and perspectives
Current Development Plan for Acute Uncomplicated Malaria

Non-clinical activity; Contribution of individual agents

Safety/tolerability of single doses; Estimated active dose range; Contribution of individual agents

Efficacy at maximum druggable dose

Dose selection rationale for Ph III

Pivotal efficacy

Drug A

- SCID mouse
- Ph Ia SAD
- Ph Ib CHMI

Ph IIa Adults dose finding

Eliminate non-viable combos

Drug B

- SCID mouse
- Ph Ia SAD
- Ph Ib CHMI

Ph IIa Adults dose finding

Ph IIb

Part 1: adults max druggable dose
Part 2: adults + children dose-finding

Ph III adults and children

Combinations (A+B, A+C, ...)

Early indication of combo efficacy

best drug combination is taken forward to Phase II and III
Computational methods – advanced pharmacometric modeling allows to estimate efficacy before Phase II

First in Human Pharmacokinetics (PK) data (drug concentration vs time)

Physiologically based pharmacokinetic (PBPK) model: Absorption, distribution, metabolism and excretion prediction for single agents and combinations

In-vitro PK interactions (for combinations)

Pharmacokinetic/pharmacodynamic (PK/PD) model: parasitemia and drug concentration vs time

Controlled Human Malaria Infection (CHMI) model (for combinations)

Key insights from pharmacometrics

- Estimate of drug efficacy and prediction of in-human dosing and cure rate
- Acceleration of progression from pre-clinical to clinical stages thanks to ranking of combinations efficacy and early identification of non-viable candidates

Severe Combined Immuno-Deficiency mouse (SCID) model (for combinations)
How does PKPD translate across the pharmacology models?

**SCID mice**
Inoculated blood stage malaria in immunodeficient mice engrafted with human red blood cells

**CHMI**
Induced blood stage malaria in healthy volunteers

**Patients**

Measurements

PK profile

PD profile

\[ K_{\text{kill}} = \frac{E_{\text{max}} C^{\text{Hill}}}{E_{\text{C50,Hill}} + C^{\text{Hill}}} \]

![Graph showing compound killing rate vs concentration](image)
### Example: Artefenomel

<table>
<thead>
<tr>
<th>SCID mouse</th>
<th>CHMI</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artefenomel</td>
<td>1 short experiment:</td>
<td>100 mg [N=8]</td>
</tr>
<tr>
<td></td>
<td>• 2 dosing regimens;</td>
<td>200 mg [N=8]</td>
</tr>
<tr>
<td></td>
<td>• over 1 week</td>
<td>500 mg [N=8]</td>
</tr>
<tr>
<td></td>
<td>1 long experiment:</td>
<td>Over one month</td>
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<tr>
<td></td>
<td>• 10 dosing regimens;</td>
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<tr>
<td></td>
<td>• over 4 weeks</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>100 mg [N=7]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg [N=15]</td>
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<tr>
<td></td>
<td></td>
<td>Over one month</td>
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</table>
PK and parasitemia are measured in each individual mice and several doses are tested.

PK and parasitemia profiles in mice after administration of Artefenomel.
A PKPD model is derived …
... and used to select the doses in CHMI study

- Population PK from FIH data
- PKPD model from SCID data

Summary across 1 populations with 1000 subjects
Compare CHMI predictions with SCID PKPD model and CHMI observations (Artefenomel)
The CHMI PKPD model is then used to predict response in patients with higher baseline parasitemia.
The PKPD model is refined with the observations in patients

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The graphs show the comparison of parasites per mL over time for two different doses: 100 mg and 500 mg. The model predictions are represented by the solid lines, while the observed data from patients are shown as black dots. The graphs illustrate the dynamics of parasite reduction over time, with model predictions and patient observations for both dosages.
Conclusion

• The animal experiments and challenge studies, combined with PKPD analysis, can help make decisions on the progression of compounds and priorities within the portfolio.

• In particular, CHMI studies lend themselves better to collect data to inform the PKPD modeling than patient trials since subtherapeutic doses can be investigated safely.
Perspectives

- Non-clinical activity; Contribution of individual agents
- Safety/tolerability of single doses; Estimated active dose range; Contribution of individual agents
- Efficacy at maximum druggable dose
- Dose selection rationale for Ph III
- Pivotal efficacy

Ph Ia
SCID mouse
Ph la SAD
Ph Ib CHMI

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Ph II
Part 1: adults max druggable dose
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adults and children

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Combinations (A+B, A+C, ...)

Drug B
C
D

Eliminate non-viable combos

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Thank you!

- MMV colleagues (Mohammed, Nada, Stephan, …)
- Partners (GSK, TAD, Swiss TPH, QIMR, IntiQuan, etc…)

[Logos of various organizations]
Backup
Impact of SCID Model on Human Doses Predictions
A reasonable predictive model compared to other disease areas

In-vivo models – SCID model help predict human dose and efficacy in pre-clinical stage

In Severe Combined Immuno-Deficiency (SCID) mouse model, mouse transfused with human blood and inoculated with *Pf* allows for in vivo testing of compounds for PK, PD, and efficacy modeling.

**Human blood inoculation to mice**

**P. Falciparum infection**

**Administer drug**

**Data collection & modelling (PK/PD)**

- **Pharmacokinetics (PK):** drug concentration vs time
- **Pharmacodynamics (PD):** parasitemia vs time
- **Modelling:** growth/kill rate vs time in response to drug concentration

**SCID models key insights**

- Estimated in-human efficacy and dosing of individual agents and combination (in preparation for CHMI studies)
- Information on how drugs work together (synergetic, additive, negative) as part of combination sciences platform to select additive/synergistic combinations

Data help predict the human dose and support compound selection.
Example of integrated impact – PK/PD Modelling of Actelion-451840 allowed an early decision to discontinue before Phase IIa

Translational capabilities use case

IBSM human challenge model:
- 8 healthy subjects inoculated with 1800 P. falciparum infected red blood cells
- Actelion-451840 500 mg administrated through oral single dose on Day 7
- Parasitemia followed closely to serve as a base to PK/PD modelling

PK/PD modelling: used to estimate parasite growth and the relation to drug exposure, with following simulations to derive estimates of likelihood of achieving cure in different scenarios

Impact

- 7 daily doses are predicted to be equivalent to artesunate monotherapy and larger doses or more frequent dosing are not predicted to achieve more rapid cure

Simulated parasite concentration for one to six doses of 500 mg once daily

Dosing allowing to reach sustained parasitemia below 1 parasite/ml

- As more than three daily doses would be needed to achieve reasonable efficacy, Actelion-451840 is unsuitable as part of a single exposure cure and has not been pushed to Phase IIa
- This allows to prioritize other most promising candidates and to save the costs of an expensive Phase II
Predicted ACPR28 (Artefenomel)

Summary across 1 populations with 1000 subjects
PK predictions with CHMI data (Artefenomel)

Summary across 1 populations with 1000 subjects
PK predictions with CHMI data (Artefenomel)
Another example: DSM265 (SCID data)
Another example with DSM265
SCID to CHMI

150 mg

400 mg

Parasites (p/mL)

Time (hours)

Model  SCID
Another example with DSM265
The PKPD model is refined with CHMI data

150 mg

400 mg
Another example with DSM265
CHMI to Patients

250 mg

400 mg

Parasites (p/mL)

Time (hours)

Model - CHMI
Another example with DSM265

• The PKPD model parameters could not be estimated with patients data only:

  Too few recrudescences were observed

• Unlike for Artefenomel, the patients trial was not aimed at identifying the MIC, ie relatively high doses, close to therapeutic doses, were tested