Induced Blood Stage Malaria: a tool to facilitate development of antimalarials

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Disclosures

• Funding from Novartis and Sanofi to support clinical trials
Outline

The method
Study endpoints
Generalisability?
Safety issues
Future options
Clinical trial design

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- **Parasite Inoculation**
- **Test drug**
- **Q-Pharm**
- **Rescue Drug Treatment as needed**

**Clearance of parasitemia over 48-96 hrs**

**n=178 subjects**
Defining the PRR and Parasite clearance $t^{1/2}$

FIG 1 Effect of lag phase and tail exclusion on the calculation of the clearance rate constant. (Modified from Flegg et al. with permission of the author.)

Marquart et al. Evaluating the pharmacodynamic effect of antimalarial drugs in clinical trials by quantitative PCR. AAC. 2015;59:4249-59
PK/PD modelling

\[ \frac{dP}{dt} = P \left( G - D \frac{c^\gamma}{c^\gamma + IC_{50}^\gamma} \right) \]

P: parasite concentration in count/ml; t: time in hr; G: the first order parasite growth rate in absence of drug; D: the maximum drug-specific parasite reduction rate; c: the drug concentration in µg/L; IC_{50}: the drug concentration required to achieve half the maximum parasite reduction rate. γ: an optional nonlinearity parameter defining the steepness of the concentration-effect curve.
How do clearance kinetics in challenge model compare to field studies?


Safety issues

• Inoculum
  – Adventitious contaminants
    • Bacteria, viruses, prions
  – Red cell alloimmunization

• Malaria
  – Malaria-induced AEs and SAEs
  – Onward Transmission
    • Gametocytemia
Safety of Inoculum

• This 3D7 blood stage *P. falciparum* line has been given to 260 human volunteers
  – 55 subjects elsewhere (Nijmegen, Oxford)
• Other blood stage *P. falciparum* strains used in IBSM
  – “Wild type” *P. falciparum* (n=2)
  – Remanufactured under GMP blood stage *P. falciparum* bank
    • 3D7 (n=2); NF54 (n=4); 7G8 (n=2)
• “Wild type” *P. vivax* (n=26)
Can we identify recrudescence and safely rescue?

Blood smear detection threshold

Drug Rx

Rescue Drug Rx

Parasites/ml

n=84 subjects

QIMR Berghofer Medical Research Institute
What is a safe treatment threshold?

- Drug potency
- Relationship between parasitemia and risk of clinical harm unknown
Can we distinguish gametocytemia from recrudescence?
Integrated Phase I and Human Challenge

- Early Safety and PK Data
- Selection of dose for early look at efficacy in human challenge
- Adaptive design
  - Kill early
  - Reformulate

Phase I
Safety & Pharmacokinetics (1 year)

Phase II
Efficacy
1-2 years

Human Challenge
6 Months

Phase I
Safety & Pharmacokinetics
1-2 years
Global Portfolio of Antimalarials

Research Lead optimization

- DHODH UTSW/UW/Monash
- Open Source Drug Discovery Univ. Sydney
- Heterocycles UCT
- Diversity Oriented Synthesis Broad/Eisai
- dUTPase Inhibitors Mediciv
- Imidazolidinediones WRAIR
- Pf NDH2 Imperial College London

1 project
- Novartis

2 projects
- GSK

Orthologue Leads Sanofi

Tetraoxanes LSTM/Liverpool

Whole cell St Jude/Rutgers/USF

Heterocycles Celgene

Pantothernamides TriasQ/RUMC/ Pansynt

16 Phase I studies (Safety & PK)
16 POC (Antimalarial activity)
120 possible combinations to be evaluated

Translational

Preclinical
- P218 (Biotec)
- DDD498 Merck (Dundee)
- PA92 (Drexel/UW/GNF)
- MMV253 (AstraZeneca)
- GSK030 GSK
- DSM421 (UTSW/UW/Monash)
- AN762 Anacor
- JPC2997 Jacobus

Human volunteers
- MMV048 UCT/TIA
- SJ733 St Jude/Eisai

Patient exploratory
- OZ439/FQ Sanofi
- KAE609 Novartis
- KAF156 Novartis
- DSM265
- Fosmidomycin Piperaquine Sevuparine Dilaforette

Patient confirmatory
- Tafenoquine GSK
- Dihydroartemisinin piperazine Paediatric Sigma-Tau
- Artemisinin Naphthoquine ** KPC
- Artemether sub-lingual spray PharmoPharma Ltd

Regulatory review
- Rectal Artesunate * Cipla/Solidex/AMR-TCR
- Artesunate for injection Guinil 1
- Dihydroartemisinin-piperazine Sigma-Tau 2
- Pyronaridine-artesunate Paediatric Shin Poong 3
- Artesunate-amodiaquine Sanofi/ UNOD 4
- Artesunate-mefloquine Cipla/NDM 5
- SPAQ Guinil 6

Access

Post approval
- Artemether-lumefantrine Dispersible Novartis
- Artesunate for injection Guinil
- Pyronaridine-artesunate Paediatric Shin Poong
- Artesunate-amodiaquine Sanofi/ UNOD
- Artesunate-mefloquine Cipla/NDM
- SPAQ Guinil

Medicines for Malaria Venture
Conclusions

• Induced blood stage malaria
  – Provides a rapid, safe and efficient means of gaining pivotal early efficacy data
  – Can be integrated into a combined Phase I PK and Safety study design
  – Provides actionable data for modelling to predict clinical dose for later stage studies
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