Defeating Malaria Together

Artefenomel/ferroquine Phase 2 Development Program

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Defeating Malaria Together
New Combinations for Case Management

**Research**
- Lead optimisation
  - Injectable Prodrug
  - Calibr
  - Miniportfolio 3 series
  - GSK
  - SFK59 series
  - H3D Cape Town
  - DHODH backups
  - UTSw/UW/Monash
- Candidate Profiling
  - Pantothenates
  - TropiC/RUMC
- Phenotypic Lead
  - Daiichi-Sankyo
- Open Source Series
  - University of Sydney
- Phe tRNA lygase
  - Broad Institute/Eisai
- Purines
  - Celgene
- DHODH
  - Broad/Eisai
- Phenotypic Lead
  - Eisai
- Molecular Target
  - DDU Dundee

**Translational**
- Preclinical
  - M5717
    - Merck KGaA
  - MMV253
    - Zydus Cadila
  - AN13762
    - (Anacor)
  - UCT943
    - H3D Cape Town
  - SAR121
    - Sanofi
- Human volunteers
  - P218
    - Janssen, (Biotech Thailand)
  - SJ733
    - Kentucky/Eisai

**Product development**
- Patient exploratory
  - Artefenomel/Ferroquine
    - Sanofi
  - MMV048
    - (UCT)
  - Cipargamin
    - Novartis
  - DSM265
    - Takeda
  - KAF156/Lumefantrine
    - Novartis
- Patient confirmatory
  - Tafenoquine
    - GlaxoSmithKline
  - Dihydroartemisinin-piperaquine
    - Paediatric
    - Sigma-Tau/Pierre Fabre
  - Cipargamin
    - Novartis
  - DSM265
    - Takeda

**Regulatory review**
- Rectal artesunate
  - Cipla/Strides/WHO-TDR

**Access**
- Post approval
  - Artemether-Lumefantrine
    - Dispersible
    - Novartis
  - Artesunate for Injection
    - Guin
  - Dihydroartemisinin-piperaquine
    - Sigma-Tau/Pierre Fabre
  - Pyronaridine-artesunate
    - Shin Poong
  - Pyronaridine-artesunate granules
    - Shin Poong
  - Artesunate-amodiaquine
    - Sanofi/DNDi
  - Artesunate-mefloquine
    - Cipla/DNDi/Farmanguinhos
  - Sulfadoxine-pyrimethamine-amodiaquine
    - Cipla/DNDi
  - Sulfadoxine-pyrimethamine-amodiaquine
    - **(Approved)
  - Rectal artesunate
    - Cipla/Strides/WHO-TDR

Footnotes:
- 🌱 Included in MMV portfolio after product approval; 🐛 Global Fund Expert Review Panel (ERP) reviewed product – permitted for time-limited procurement, while regulatory/WHO prequalification review is ongoing. 🌱 WHO Prequalified OR approved/positive opinion by regulatory bodies who are ICH members/observers.
- MMV support to projects may include financial, in-kind, and advisory activities.
Artefenomel-Ferroquine

Two independent mechanisms of action, active against resistance


Ferroquine + artefenomel: potential to shorten therapy and overcome resistance
Artefenomel Kills Artemisinin Resistant Strains

Table 1 Mean per cent survival (individual values in brackets) of Cam3.1^{RS39T} isolate after 6 h exposure to a range of concentrations of DHA, OZ439 or OZ277 using the synchronization protocol from Xie et al. [53]

<table>
<thead>
<tr>
<th>Compounds</th>
<th>RSA values (% survival) at different concentrations</th>
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<tbody>
<tr>
<td></td>
<td>175 nM</td>
</tr>
<tr>
<td>DHA</td>
<td>46 (49,43)</td>
</tr>
<tr>
<td>OZ277</td>
<td>4.0 (4.4, 3.6)</td>
</tr>
<tr>
<td>OZ439</td>
<td>&lt;0.01 (&lt;0.01, &lt;0.01)</td>
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</tbody>
</table>

Artefenomel in Controlled Human Malaria Infection (HCMI) Model

500 mg dose causes 10,000-fold drop in parasites over 48 h, a parasite half-life of 3.6 h

Artefenomel in Patients

Parasite clearance half lives were 4.1–5.3 h for *P. falciparum* and 2.3–3.2h for *P. vivax*

Activity in Patients with Artesunate Resistance


Figure 3: Parasite clearance and kelch mutations
Clearance times for patients infected with parasites with kelch mutations or wild-type. The horizontal line represents the median.
Ferroquine in CHMI Model

800 mg FQ: 162-fold reduction in 48 h; half life = 6.5 h
Time above Minimal Parasiticidal Concentration = 454 h

### Ferroquine in Patients

#### PP population

<table>
<thead>
<tr>
<th>FQ/AS (daily dose)</th>
<th>FQ alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>n total = 325 patients</td>
<td>2 mg/kg ( (100\text{mg}) ) (n=70)</td>
</tr>
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</table>

#### PCR corrected ACPR at Day 28*

<table>
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<th>FQ/AS (daily dose)</th>
<th>FQ alone</th>
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</thead>
<tbody>
<tr>
<td>68/70 91.7%</td>
<td>74/74 100.0%</td>
</tr>
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</table>

#### 95% Clopper-Pearson CI

<table>
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<tr>
<th>FQ/AS (daily dose)</th>
<th>FQ alone</th>
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</thead>
<tbody>
<tr>
<td>90.0–99.7</td>
<td>95.1–100.0</td>
</tr>
</tbody>
</table>

Parasite clearance times only reported for FQ/AS groups

Artefenomel-Ferroquine

Artefenomel (OZ439)
- Novel aromatic trioxolane
- “Fast” killer & high efficacy on parasite clearance
- No cross resistance
- Intermediate half life (4–5 days)

Ferroquine (SSR97193)
- 4 aminoquinoline
- “Slow” Killer with sustained sterilization
- No cross resistance
- Long half life (>30 days; >40 days for active metabolite)

Ferroquine + artefenomel: potential to shorten therapy and overcome resistance

Artefenomel-ferroquine: Phase 2b ‘FALCI’ Trial

«A randomized, double blind, study to investigate the efficacy, safety, tolerability and pharmacokinetics of a single dose regimen of ferroquine (FQ) with Artefenomel (OZ439) in adults and children with uncomplicated Plasmodium falciparum malaria»

- Locations: 17 sites in 7 countries (6 in Africa, 1 in Asia)
- Sample Size: up to 662 (4 treatment arms)
- IMP formulations (oral): FQ capsules, artefenomel+TPGS in sachets
- Completion in early 2019: Dosing 5–14 yo’s completed; next step 2–5 yo’s

For patients ≥35 kg, 4 doses of FQ will be assessed along with a fixed dose of OZ439; Weight-adjusted doses for OZ439 & FQ for patients < 35 kg

- FQ at 400 mg and OZ439 800 mg OD in single dose
- FQ at 600 mg and OZ439 800 mg OD in single dose
- FQ at 900 mg and OZ439 800 mg OD in single dose
- FQ at 1200 mg and OZ439 800 mg OD in single dose
Artefenomel-ferroquine: Remaining Phase 2 Program

- Additional Phase 2 trial to fulfill ‘combination rule’ requirement
  - FQ dose held constant and OZ439 dose varied
  - Design based on measuring exposure response
  - Sites overlapping with FALCI sites
  - Launch in Q1 2018; completion in 2019

- Additional optimization work to hone in on best formulation for Phase 3
Conclusions

- OZ439 & FQ – two novel agents with different MoA’s deep in Phase 2 development
- Encouraging clinical data generated on both molecules as mono-therapies (CHMI model & clinical trials) and in combination trials
- Modelling/simulation of doses required to cure non-immune patients suggests single dose cure may be achievable
- Randomized, double-blind, Phase 2b ‘FALCI’ trial to test combination in patients as young as 6 mos. underway in 17 sites
- Additional randomized trial to fulfill requirement for combination rule (FQ set dose; OZ439 varied dosing) to launch in Q1 2019
- Formulation work to optimise exposure of artefenomel as pathway to formulation selection for Phase 3 is ongoing in parallel