Synthetic Peroxides: A Viable Alternative to Artemisinins

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ARTEMISININ FORUM 2009
Mumbai, 30 Sep 2009

Curing Malaria Together
www.mmv.org
Role of Artemisinins in the Treatment of Malaria

• Artemisinin derivatives are now the mainstay of treatment for malaria

• Heavy reliance on the artemisinin component:
  • fast acting, highly effective against both *P. falciparum* and *P. vivax*
  • rapidly cleared; used in combination with a longer-acting partner drug

• But there are issues...
  • supply, cost, natural source
  • any clinical resistance to artemisinin will jeopardize ACT strategies
  • concerns regarding use in some special populations (infants, pregnancy)
Alternative Sources of Artemisinin / plant derived peroxides

- One World Health, Amyris, Berkeley & Sanofi
- Dafra / Bouwmester (chicory)
- Plant cell culture system (Russia, Japan and others)
- Tobacco (Swiss)
- Cameroon (Plant families)
Fully Synthetic Peroxides

- Arterolane (OZ277/RBx11160), Ranbaxy: Phase III
- OZ439, MMV: Phase I
- CDRI97/73, CDRI/IPCA : Phase I
- Trioxaquine® (SAR116242), Sanofi: Candidate
- RKA182, University of Liverpool : Candidate
MMV’s peroxide portfolio

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### Introduction to MMV
Innovation in discovery development and delivery

<table>
<thead>
<tr>
<th>Research</th>
<th>Lead Gen</th>
<th>Lead Opt</th>
<th>Preclinical</th>
<th>Translational Phase I</th>
<th>Phase II</th>
<th>Development Phase III</th>
<th>Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis</td>
<td>3 projects</td>
<td>KAC776 Novartis</td>
<td>MK 4815</td>
<td>Pyridone 121</td>
<td>IV artesunate Guilin</td>
<td>Pyramax® Shin Poong/University of Iowa</td>
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<td>GSK</td>
<td>3 projects</td>
<td>Pyridones GSK</td>
<td>KAC470 Novartis</td>
<td>Tafenoquine</td>
<td>Artemisone UHKST</td>
<td>Coarsucam sanofi-sventis</td>
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<td>3 projects</td>
<td>DHODH UTSW/UW/Monash</td>
<td>P218 BIOTEC/Monash/LSHTM</td>
<td>OZ 439 Monash/UNMC/STI</td>
<td>(-) Mefloquine Treague</td>
<td>Eurartesim™ sigma-tau</td>
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<td>Immucillins</td>
<td>Albert Einstein</td>
<td>Aminoindoles Broad/ Genzyme</td>
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<td>Myosin Motor</td>
<td>Drexel/UW</td>
<td>Ozonide Monash/UNMC/STI</td>
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<td>Quinolones</td>
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<td>ELQs</td>
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<td>Other Screening</td>
<td>18 Projects</td>
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Eurartesim submitted on July 3rd 2009 to EMEA
Pyramax to be submitted March 2010 to EMEA
Four new molecules started phase I
MMV peroxide portfolio

- One ACT registered
- One ACT submitted for registration
- One ACT submission in preparation
- Artemisinin Resistant Testing
  - Testing our endoperoxide collections against primary parasites from resistance areas (Laos, Cambodia, Thailand, Senegal) (ex vivo)
  - Clinical testing of novel endoperoxides in patients where PCT is increased: Artemisone and future peroxide candidates
- Ozonides (OZ439)
MMV aims for synthetic peroxides

• Active against Artemisinin resistant malaria
• Safe in early stage pregnancy
• Improved PK characteristics (longer $t_{1/2}$)
• More potent than the currently available semi-synthetic artemisinin derivatives in reducing parasite burden
• Provision in combination of a single-dose oral cure for patients with uncomplicated P. falciparum malaria (and possibly P. vivax)
• Potential for intermittent preventative treatment in pregnant women and infants (IPTp and IPTi)
• CoG to meet MMV‘s target treatment price <1$
Key Pharmacology for OZ439: 
*Plasmodium berghei* Mouse Model (p.o.)

Single oral dose: 1x 30 mg/kg p.o.

<table>
<thead>
<tr>
<th>Compound (30 mg/kg)</th>
<th>Activity (%)†</th>
<th>Survival (d), Cure (%)‡</th>
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<tbody>
<tr>
<td>AS</td>
<td>92</td>
<td>9 d, 0%</td>
</tr>
<tr>
<td>AM</td>
<td>99.7</td>
<td>9 d, 0%</td>
</tr>
<tr>
<td>CQ</td>
<td>99.9</td>
<td>10 d, 0%</td>
</tr>
<tr>
<td>MEF</td>
<td>99.6</td>
<td>22 d, 0%</td>
</tr>
<tr>
<td>OZ277</td>
<td>99.9</td>
<td>11 d, 0%</td>
</tr>
<tr>
<td>OZ439</td>
<td>99.0</td>
<td>&gt;30 d, 100%</td>
</tr>
<tr>
<td>Control</td>
<td>--</td>
<td>6 d, 0%</td>
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</tbody>
</table>

† % parasitemia on day 3 post infection
‡ % of mice that were parasite free on day 30

Onset & Recrudescence: 1x 100mg/kg p.o.

AS, AM, CQ and MEF do not cure in this model up to 200 mg/kg.
In Vitro Degradation in Infected Blood

- OZ439 is stable in not-infected and infected blood

![Graph showing OZ439 stability in both healthy and infected blood](image)

- Healthy blood
- Infected blood (1% parasitemia)
Development Plan

- **Completed**
  - Phase I SRD 50 to 1600 mg

- **Ongoing:**
  - Phase I MRD: 3x 200, 400, 800 mg
  - Phase I Food Effect: 800 mg fed and fasted
  - Reprotox segment II
  - Preliminary formulation work with long $t_{1/2}$ antimalarials

- **Planned**
  - Phase II PoC monotherapy (Q4/09/Q1/10)
  - Phase II Region of Artemisinin Resistance (2010)
  - Phase II combination
Timelines Phase II DRF Combination

Dose ranging with combination product
Timelines Phase II DRF Monotherapy + Combo

Dose ranging with single agent followed by combination phase II
Conclusions

• 1 combination with an existing partner drug

• Preparing discussions with regulatory agency on development plan

• Intended to develop 2nd combination with suitable NCE when available

• Registration expected by 2013-2015