Synthetic Peroxides:
A Viable Alternative to Artemisinins

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

• Artemisinin derivatives are now the mainstay of treatment for malaria

• Since WHO endorsement of Artemisinin-based Combination Therapy (ACT) as 1st or 2nd line therapy for uncomplicated *P. falciparum* 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)
Known Artemisinin Programmes

• Alternative Sources of Artemisinin / plant derived peroxides
  • One World Health, Amyris, Berkeley (yeast)
  • Dafra / Bouwmester (chicory)
  • Plant cell culture system (Russia, Japan and others)
  • Tobacco (Swiss)
  • Cameroon (Plant families)

• Fully Synthetics
  • Arterolane (OZ277/RBx11160), Ranbaxy (phase III)
  • University of Liverpool, (ANTIMAL programme) (candidate)
  • Ozonides OZ439 (MMV) (phase I)
## MMV Malaria Portfolio
### November 2008

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<td>MK 4815</td>
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<td>DHODH</td>
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<td>Immucillins</td>
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<td>Einstein</td>
<td>Biartemides</td>
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<td>NITD</td>
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**Note:**
- DHFR: Dihydrofolate Reductase
- NITD: Novel Insecticidal Traits Domain
- DHODH: Dihydroorotate Dehydrogenase
- Nat Product: Natural Products
- Immucillins: Immucillins
- Biartemides: Biartemides

**Medicines for Malaria Venture**
MMV peroxide portfolio

- One ACT submitted for registration
- Two ACT and one mono-therapy currently in clinical trials
- Artemisinin Resistance Network

  - Testing our endoperoxide collections (8) against primary parasites from resistance areas (Laos, Cambodia, Thailand, Senegal) (ex vivo)
  - Clinical testing of novel endoperoxides in patients where PCT is increased: Artemifone

- Ozonides
Objectives: Synthetic Peroxides (OZ) Project

• **First Generation OZ project aimed to:**
  - identify a new class of peroxides
  - more potent than the currently available semi-synthetic artemisinin derivatives in reducing parasite burden
  - fully synthetic
  - low cost (< $1 USD per treatment when used in combination)
  - 3 day treatment regimen when used in combination

• **Next Generation OZ project extends these goals to also include:**
  - provision in combination of a single-dose oral cure for patients with uncomplicated *P. falciparum* malaria (and possibly *P. vivax*)
  - potential for prophylactic treatment and intermittent preventative treatment in pregnant women and infants (IPTp and IPTi)
First Generation of Synthetic Peroxides

OZ277 or RBx11160
What do we know about RBx11160?

- More active than chloroquine, mefloquine, and artemisinin derivatives against *P. falciparum in vitro*, and *P. berghei* in mice
- Good physicochemical and metabolic profile; good PK and oral bioavailability in rats and dogs; short half-life
- Excellent safety profile in rats, dogs and humans after single and repeat administration
- Similar exposure after single and repeat administration in humans; minimal food effects
Phase 1 Plasma Concentrations of RBx11160

Plasma concentrations after a single oral dose to healthy volunteers

- Excellent exposure at doses of 100 mg or above…
- Highly consistent with predictions based on animal data, but …
“Issues” that Arose with RBx11160 in Phase 2

- Significant reduction in drug plasma concentrations in malaria patients...
- Reduced exposure meant that it was unlikely to meet 3-day treatment regimen
- Phase II: Approx 70% efficacy (28 ACPR) with 7 days treatment
In Vitro Degradation in Infected Blood

- Rapid *in vitro* degradation of RBx11160 in infected blood

![Graph showing in vitro degradation comparison between healthy and infected blood](image)
Second Generation of Synthetic Peroxides
Clearance in Red Blood Cells

• Fe(II)-mediated cleavage likely to be a significant contributor to the \textit{in vivo} clearance of RBx11160

• Can we modify the ozonide structure to reduce the rate of cleavage without compromising biological activity?

• The answer is... \textbf{Yes}
Ozonide Clearance in Red Blood Cells

• **Next Generation OZ are significantly more stable in whole blood *in vitro* than First Generation OZ**

![Graph showing % Remaining in Whole Blood vs Time (min) for Next Generation OZ and RBx 11160](image)
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>
</tr>
</thead>
<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>
</tr>
</tbody>
</table>

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

AS, AM, CQ and MEF do not cure in this model up to 200 mg/kg.
## Dosing Regimen and Survival

<table>
<thead>
<tr>
<th>Dose</th>
<th>Frequency</th>
<th>Avg Survival</th>
<th>Cures</th>
</tr>
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<tbody>
<tr>
<td>1 x 1 mg/kg</td>
<td>single</td>
<td>6</td>
<td>0/5</td>
</tr>
<tr>
<td>1 x 3 mg/kg</td>
<td>single</td>
<td>6</td>
<td>0/5</td>
</tr>
<tr>
<td>1 x 5 mg/kg</td>
<td>single</td>
<td>10.4</td>
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<tr>
<td>1 x 10 mg/kg</td>
<td>single</td>
<td>18.2</td>
<td>0/5</td>
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<tr>
<td>1 x 15 mg/kg</td>
<td>single</td>
<td>30</td>
<td>4/5</td>
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<tr>
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<tr>
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<td>every 24 h</td>
<td>6</td>
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<td>3 x 3 mg/kg</td>
<td>every 24 h</td>
<td>15.2</td>
<td>0/5</td>
</tr>
<tr>
<td>2 x 5 mg/kg</td>
<td>every 24 h</td>
<td>14.6</td>
<td>0/5</td>
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<tr>
<td>3 x 5 mg/kg</td>
<td>every 24 h</td>
<td>&gt;30</td>
<td>5/5</td>
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<tr>
<td>2 x 10 mg/kg</td>
<td>every 24 h</td>
<td>&gt;30</td>
<td>5/5</td>
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<td>&gt;30</td>
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<td>&gt;30</td>
<td>5/5</td>
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In Vitro Degradation in Infected Blood

- Next Generation OZ significantly more stable in healthy and especially infected blood.
OZ439 Exposure in Healthy and Infected *P. berghei* Mice

10 mg/kg po

Approximately 50% decrease in exposure in presence of infection

Half life still > 5-fold longer than that of OZ277 and Art derivatives at similar dose
Conclusions

• Fe(II)-mediated cleavage in RBCs contributes to the \textit{in vivo} clearance of RBx11160 (and possibly other peroxides)

• \textbf{Structural modifications for Next Generation OZ have resulted in:}
  – improved stability in blood
  – reduced \textit{in vivo} clearance, prolongation in half-life and increased exposure in rats
  – enhanced biological activity in well-established mouse model of malaria
  – excellent prophylactic activity in mice – exceeds that of the benchmark chemoprophylactic, mefloquine

• \textbf{Potential for reduced treatment regimen}
Timelines

Launch → Q4 2013
Partners

• Medicinal and synthetic chemistry
  University of Nebraska, USA
• *In vitro* activity and *in vivo* efficacy assessment
  Swiss Tropical Institute, Switzerland
• ADME, lead optimisation and compound profiling
  Monash University, Australia
• Manufacturing and Formulation
  Unimark Remedies, India, Wilmington Pharma, USA, Penn Pharmaceuticals UK
• Project management and Consultants
  Fulcrum, UK, Carl Craft and John Scott, USA
• Medicines for Malaria Venture
  Ian Bathurst and Jörg Möhrle
Thank you

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