Potential impact of new drug development
Synthetic Peroxides: A Viable Alternative to Artemisinins

25 June 2007 Bangkok
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:

- strategy has been adopted by 69 countries
- forecast for 2007 of 150 million treatments

- 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)
What is MMV

• A not for profit organisation
• Creation of MMV in 1999 by
  • WHO
  • The World Bank
  • Donor governments (CH, UK)
  • Philanthropic foundations
  • IFPMA
MMV's overall objective is to ensure the sustainable and continuous generation of appropriate new malaria medicines that are accessible to those in need in developing countries at the lowest prices practicable.

- **APPROPRIATE**
- **AFFORDABLE**
- **ACCESSIBLE**
Objectives of the Synthetic 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 Peroxices

OZ277 or RBx11160
What do we know about RBx 11160?

• More active than CQ, MF, 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; half-life shorter than desired

• 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 RBx 11160

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 …

In vitro concentration required for 50% parasite inhibition
"Issues" that Arose with RBx 11160 in Phase 2

- Significant reduction in plasma concentrations in malaria patients...
- Such reduced exposure meant unlikely to meet 3-day treatment regimen
Clinical Study MMV05-06 of RBx11160 Monotherapy:

- A Phase II, Dose-Ranging Study with RBx 11160 Administered for 7 Days in 230 Patients With Acute Uncomplicated *Plasmodium falciparum* Malaria was recently concluded.
- Analysis is ongoing
- Early results show that the cure rate (PCR corrected ACPR) is well below MMV’s target (90% efficacy) for individual components of a combination product.
Possible “first cut” explanations:

- time of dosing no effect
- postural differences no effect
- ethnic differences in metabolism no effect

Differences due to the presence of the infection:

- definition of clearance mechanisms for RBx 11160 (and the resulting affect on plasma concentrations)
- exploration of the blood stability *in vitro ± parasites*
OZ Clearance in Red Blood Cells (RBC)

- RBC contains **haemoglobin** - Fe(II) haem
- Cleavage of peroxide by Fe(II)-containing components in RBC
- Cleavage contributes to clearance from the circulation

![Chemical structure of RBx 11160](image)
First Generation OZ exhibited relatively rapid degradation in whole blood \textit{in vitro}.
In Vitro Degradation in Infected Blood

- Rapid *in vitro* degradation of RBx 11160 in **infected blood**

![Graph showing the degradation of RBx 11160 over time in healthy and infected blood. The graph includes a line for healthy blood and a line for infected blood with 1% parasitemia. The x-axis represents time in minutes (0 to 240), and the y-axis represents the percentage of initial remaining. The graph shows a significant difference in degradation between the two types of blood.](image-url)
Second Generation of Synthetic Peroxides
OZ Clearance in Red Blood Cells

- Fe(II)-mediated cleavage likely to be a significant contributor to the *in vivo* clearance of RBx 11160

- Can we modify the OZ structure to reduce the rate of cleavage without compromising biological activity?

- The answer is... *Yes*
OZ Clearance in Red Blood Cells

- Next Generation OZ are significantly more stable in whole blood *in vitro* than First Generation OZ
Increased Stability of Next Generation OZs

- Greater stability in blood contributes to better exposure, longer half-life…and biological activity is better!

10 mg/kg Oral Dose to Rats

Plasma Concentration (ng/mL) vs. Time (h)
Increased Stability of Next Generation OZs

- Greater stability in blood contributes to better exposure, longer half-life... and biological activity is better!

10 mg/kg Oral Dose to Rats

**Time (h)**

0 6 12 18 24 30 36 42 48

**Plasma Concentration (ng/mL)**

0.1 1 10 100 1000 10000

**Next Generation OZ**

**RBx 11160**

**In vitro concentration for 50% parasite inhibition**
Antimalarial Activity in Mice

Single 30 mg/kg oral dose to mice (*P. berghei*)

<table>
<thead>
<tr>
<th>Compound (mg/kg)</th>
<th>Survival (d), Cure (%)</th>
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</thead>
<tbody>
<tr>
<td>Artesunate</td>
<td>9 d, 0%</td>
</tr>
<tr>
<td>Artemether</td>
<td>9 d, 0%</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>10 d, 0%</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>22 d, 0%</td>
</tr>
<tr>
<td>RBx 11160</td>
<td>11 d, 0%</td>
</tr>
<tr>
<td>No treatment</td>
<td>6 d, 0%</td>
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Limited survival; no cures with artemisinin derivatives, conventional drugs or RBx 11160
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Single 30 mg/kg oral dose to mice (\textit{P. berghei})

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<td>OZ401</td>
<td>25 d, 64%</td>
</tr>
<tr>
<td>Artemether</td>
<td>9 d, 0%</td>
<td>OZ439</td>
<td>&gt;30 d, 100%</td>
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<tr>
<td>Chloroquine</td>
<td>10 d, 0%</td>
<td>OZ460</td>
<td>25 d, 60%</td>
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<td>OZ482</td>
<td>&gt;30 d, 100%</td>
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<td></td>
<td></td>
<td>OZ485</td>
<td>25 d, 40%</td>
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<td></td>
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<td>OZ493</td>
<td>&gt;30 d, 100%</td>
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Survival and 100% cure for Next Generation OZ
Prophylaxis in Mice

30 mg/kg given 24 h prior to *P. berghei* infection (mice)

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Only mefloquine has prophylactic properties
**Prophylaxis in Mice**

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Three next generation OZ are 100% prophylactic and are superior to mefloquine.
OZ Cleavage Accelerated in Infected Blood

Infected RBC

- High concentrations of Fe(II) haem in the parasite
- Rapid cleavage of RBx11160 in the presence of parasites

Fe(II) cleavage in RBC cytosol

Fe(II)-mediated processes in parasite

inactive cleavage products

Parasite death

inactive cleavage products

competing processes in infected RBCs are not well defined
In Vitro Degradation in Infected Blood

- Next Generation OZ significantly more stable in healthy and especially infected blood.

**Graphs**
- **RBx 11160**: Shows degradation over time in healthy blood and infected blood (1% parasitemia).
- **Next Generation OZ**: Demonstrates stability in both healthy and infected blood (1% parasitemia).
Conclusions

• Fe(II)-mediated cleavage in RBCs contributes to the *in vivo* clearance of RBx 11160 (and possibly other peroxides)

• Structural modifications for Next Generation OZ have resulted in:
  – improved stability in blood
  – reduced *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 (Lariam®)
Timelines

Launch > Q3 2013
Partners

- Medicinal and synthetic chemistry
  University of Nebraska
- *In vitro* activity and *in vivo* efficacy assessment
  Swiss Tropical Institute, Basel
- ADME, lead optimisation and compound profiling
  Monash University
- Project management and funding
  MMV