Synthetic Peroxides:

A Viable Alternative to Artemisinins

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ARTEMISININ FORUM 2008

Guilin, 11 Nov 2008

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)

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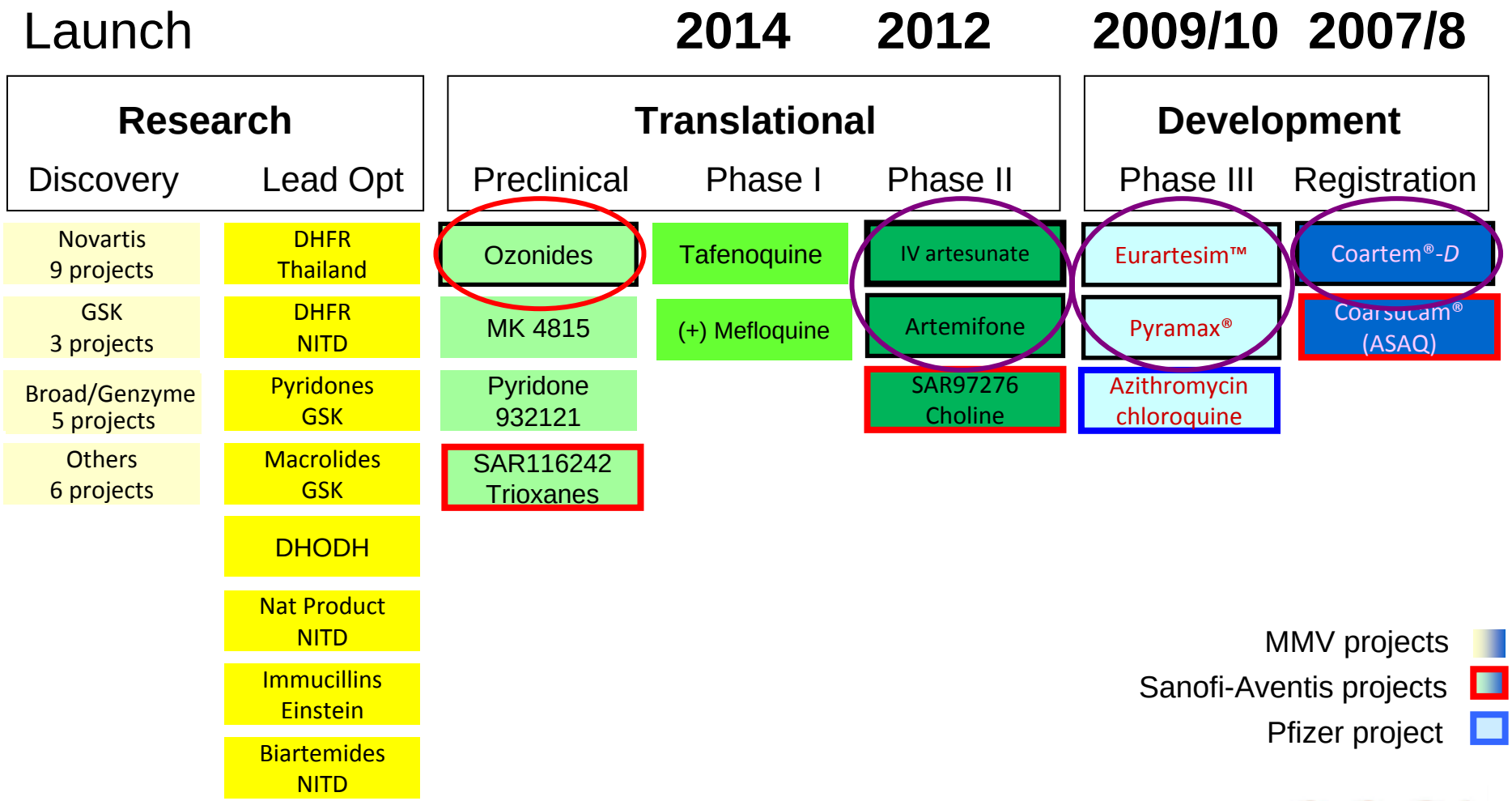
Known Artemisinin Programmes

- 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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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

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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)

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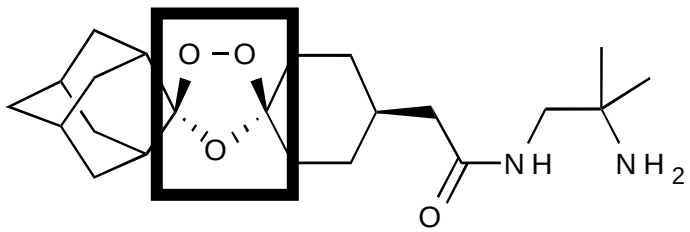
First Generation of Synthetic Peroxides

OZ277 or RBx11160



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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**

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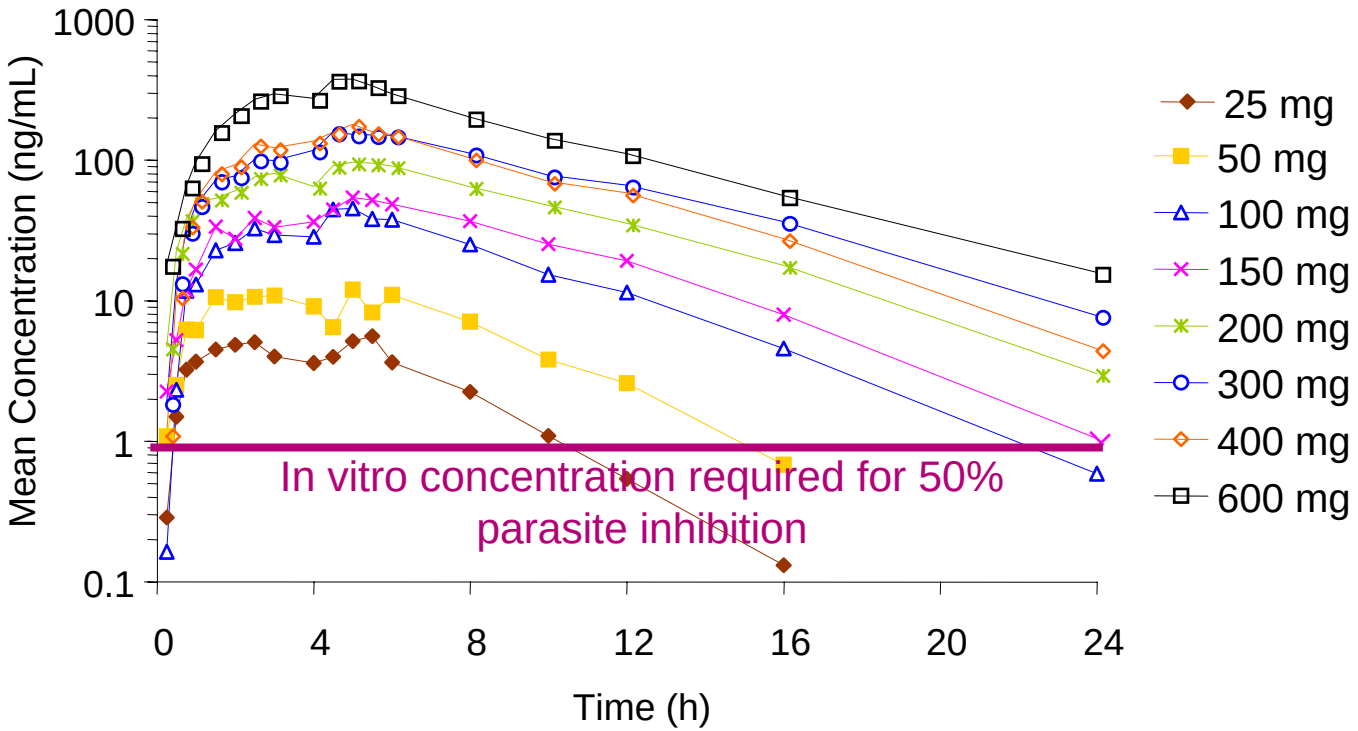
Phase 1 Plasma Concentrations of RBx11160

Plasma concentrations after a single oral dose to healthy



- Excellent exposure at doses of 100 mg or above...
- Highly consistent with predictions based on animal data, but ...

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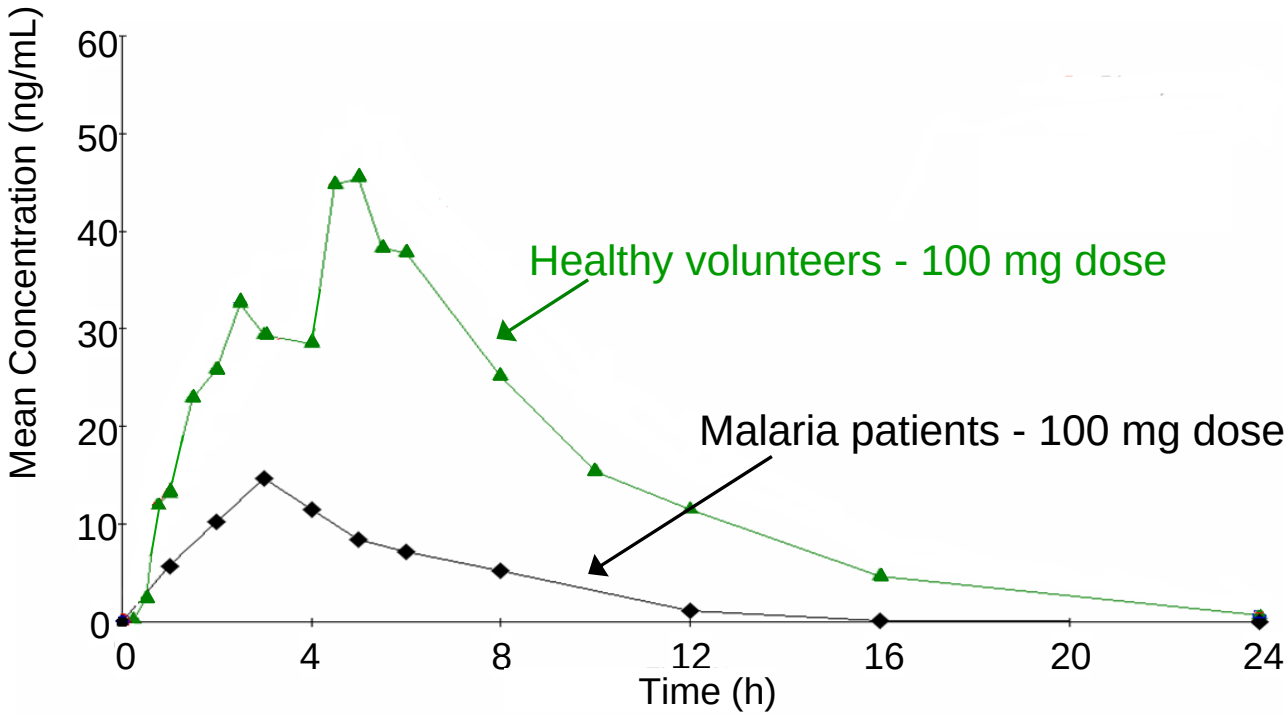
“Issues” that Arose with RBx11160 in Phase 2



- **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**

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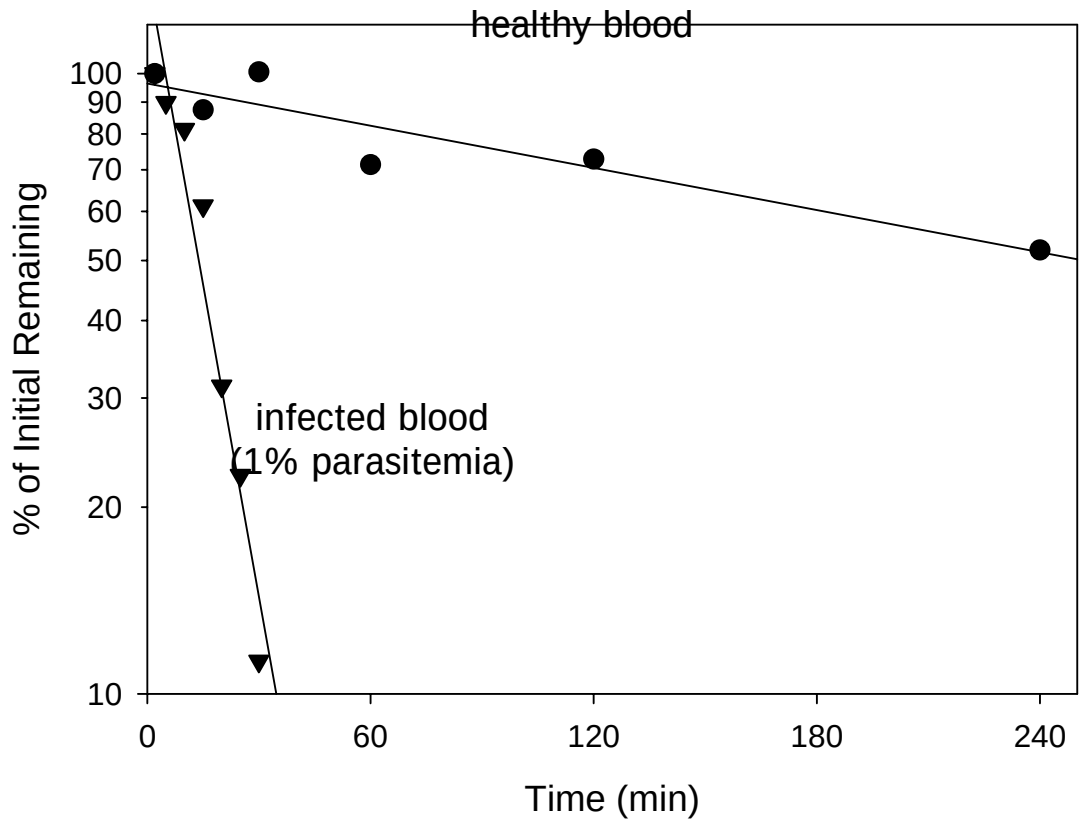
In Vitro Degradation in Infected Blood

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



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Second Generation of Synthetic Peroxides

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Clearance in Red Blood Cells

- **Fe(II)-mediated cleavage likely to be a significant contributor to the *in vivo* clearance of RBx11160**
- **Can we modify the ozonide structure to reduce the rate of cleavage without compromising biological activity?**
- **The answer is…** **Yes**

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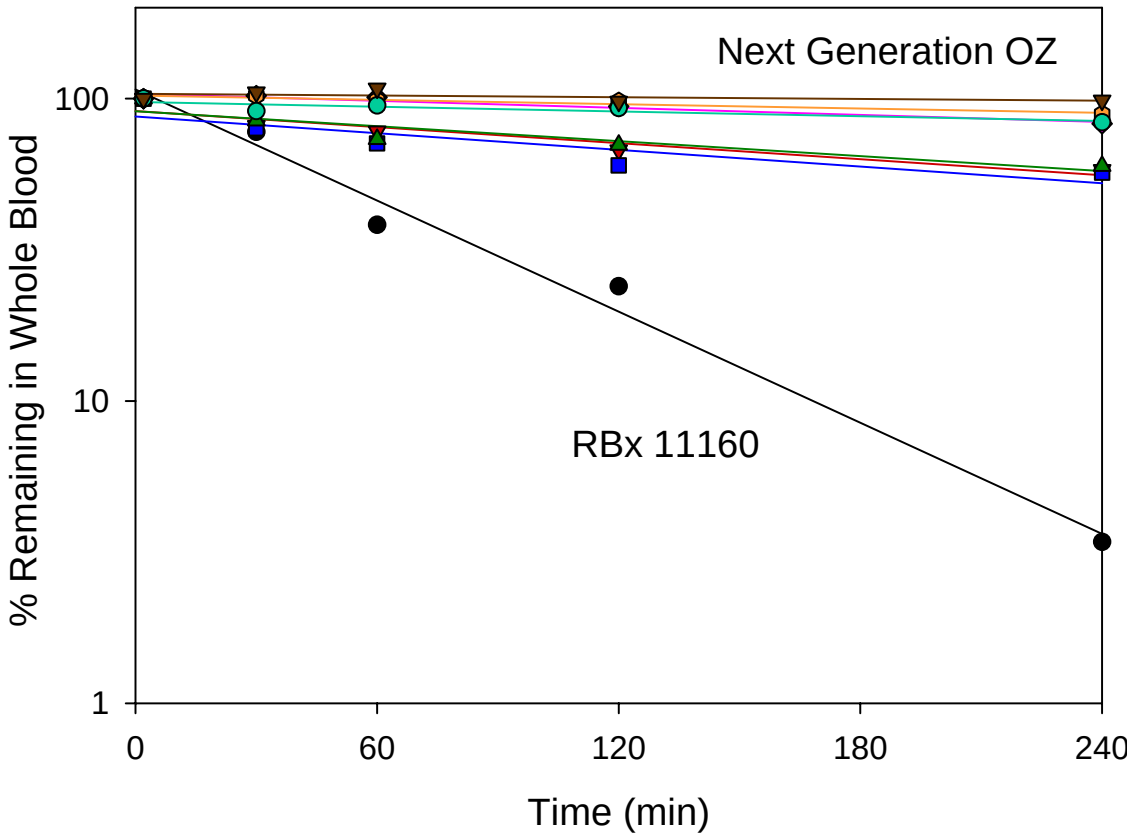
Ozonide Clearance in Red Blood Cells

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



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Key Pharmacology for OZ439: *Plasmodium berghei* Mouse Model (p.o.)

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

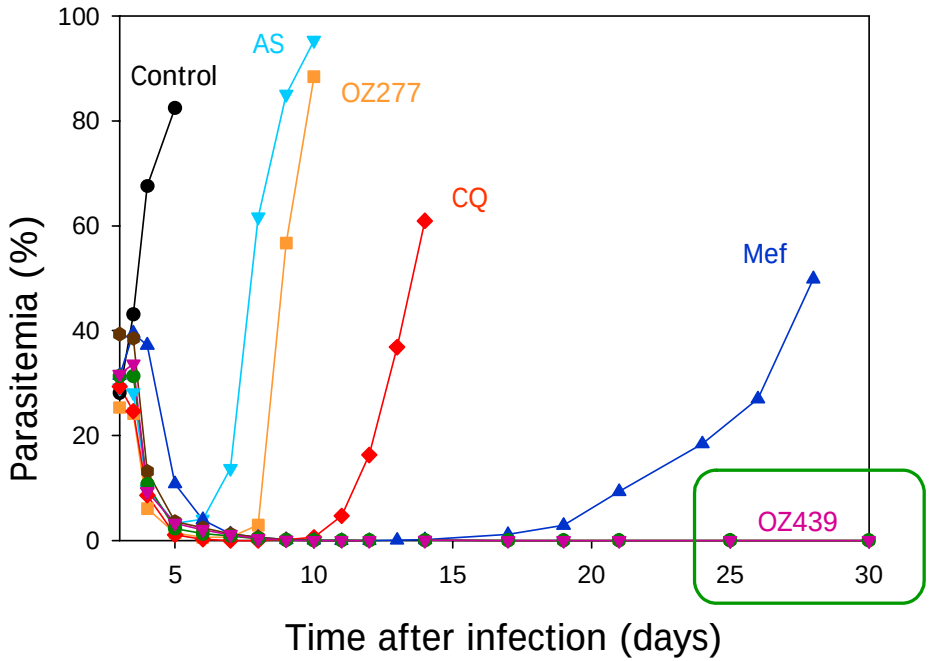
Compound (30 mg/kg)	Activity (%)†	Survival (d), Cure (%)‡
AS	92	9 d, 0%
AM	99.7	9 d, 0%
CQ	99.9	10 d, 0%
MEF	99.6	22 d, 0%
OZ277	99.9	11 d, 0%
OZ439	99.0	>30 d, 100%
Control	--	6 d, 0%

† % 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.

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



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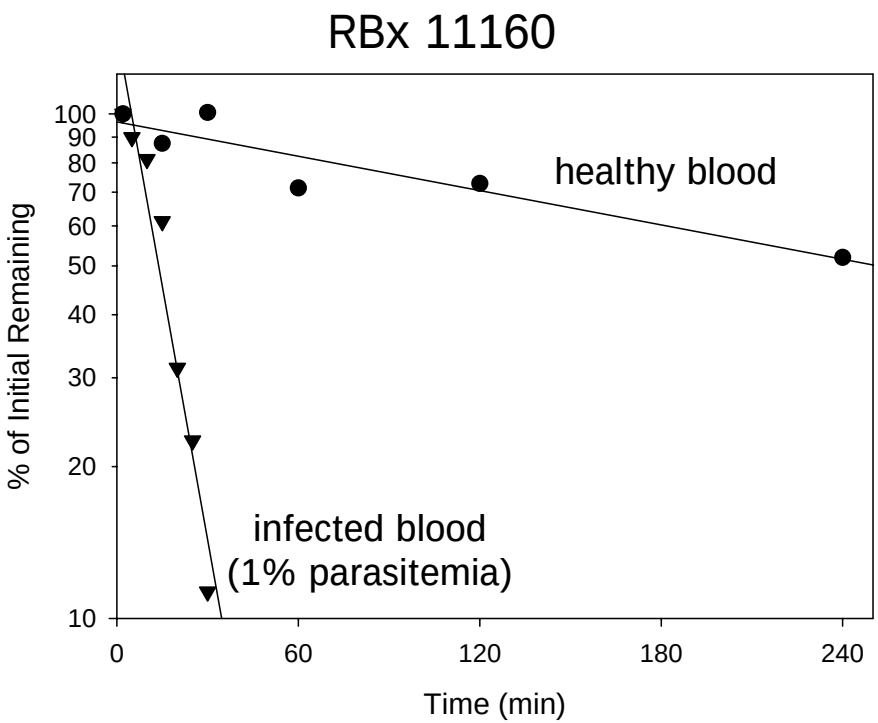
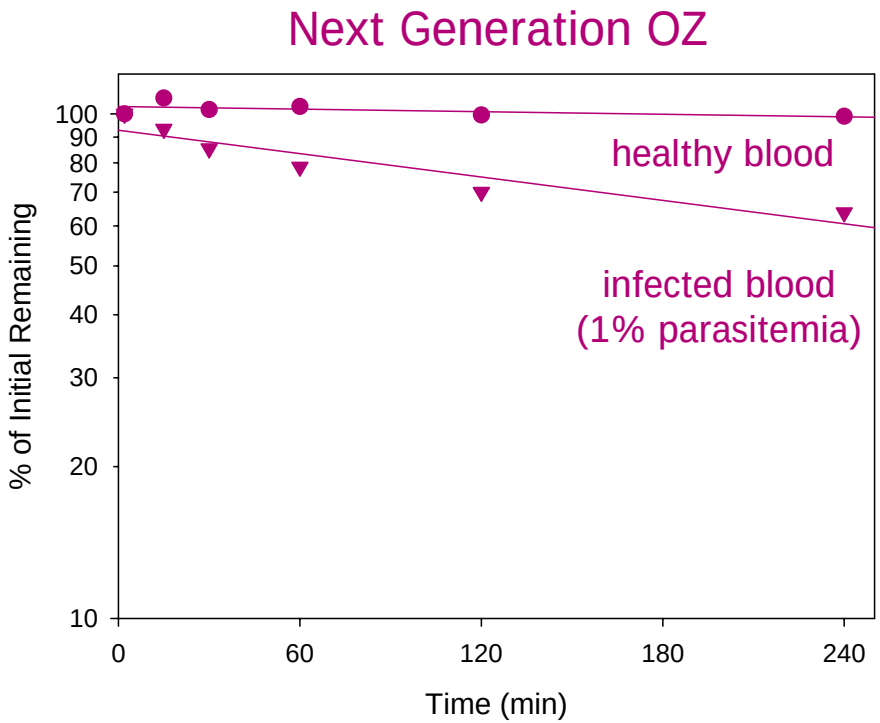
Dosing Regimen and Survival

Dose	Frequency	Avg Survival	Cures
1 x 1 mg/kg	single dose	6	0/5
1 x 3 mg/kg	single dose	6	0/5
1 x 5 mg/kg	single dose	10.4	0/5
1 x 10 mg/kg	single dose	18.2	0/5
1 x 15 mg/kg	single dose	30	4/5
1 x 20 mg/kg	single dose	>30	5/5
1 x 25 mg/kg	single dose	>30	5/6
1 x 30 mg/kg	single dose	>30	5/7
3 x 1 mg/kg	every 24 h	6	0/5
3 x 3 mg/kg	every 24 h	15.2	0/5
2 x 5 mg/kg	every 24 h	14.6	0/5
3 x 5 mg/kg	every 24 h	>30	5/5
2 x 10 mg/kg	every 24 h	>30	5/5
3 x 10 mg/kg	every 24 h	>30	5/5
3 x 3 mg/kg	every 12 h	12.2	0/5
3 x 5 mg/kg	every 12 h	28.2	4/5
2 x 10 mg/kg	every 12 h	>30	5/5
3 x 10 mg/kg	every 12 h	>30	5/5
2 x 15 mg/kg	every 12 h	>30	5/5
2 x 20 mg/kg	every 12 h	>30	5/5

In Vitro Degradation in Infected Blood

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





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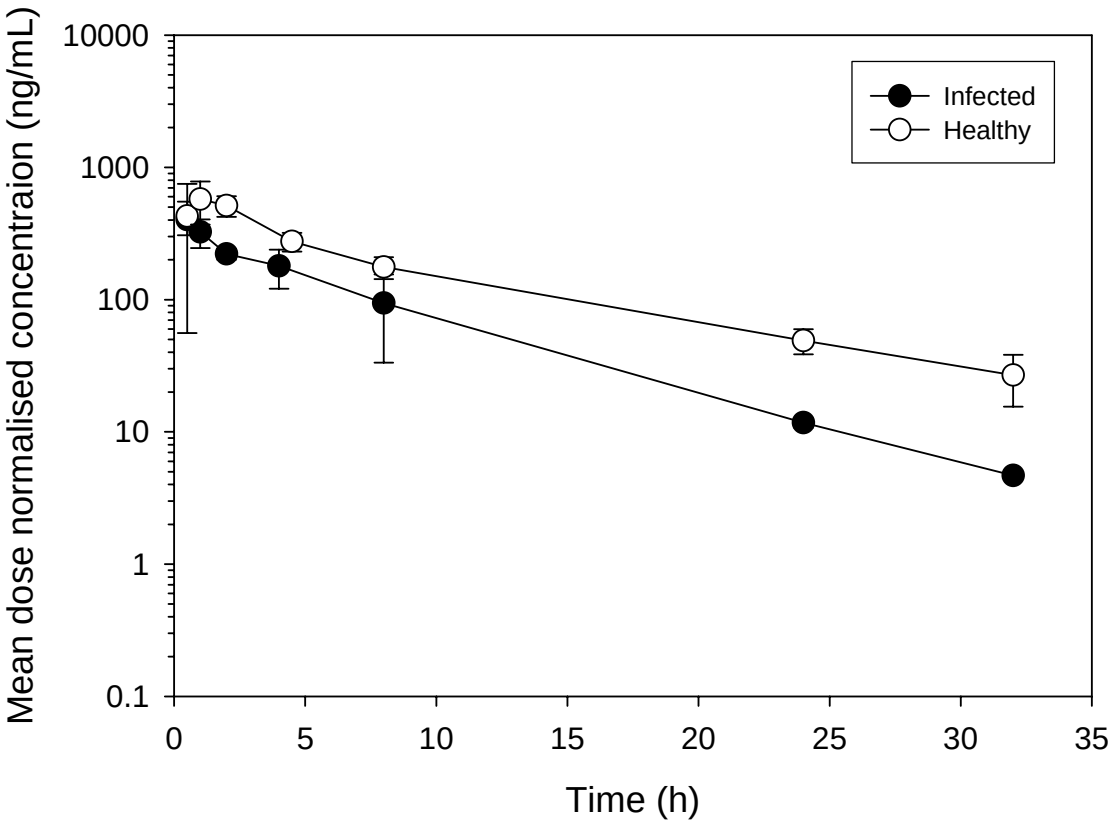
OZ439 Exposure in Healthy and Infected *P. berghei* Mice



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

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Conclusions

- **Fe(II)-mediated cleavage in RBCs contributes to the *in vivo* clearance of RBx11160 (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
- **Potential for reduced treatment regimen**

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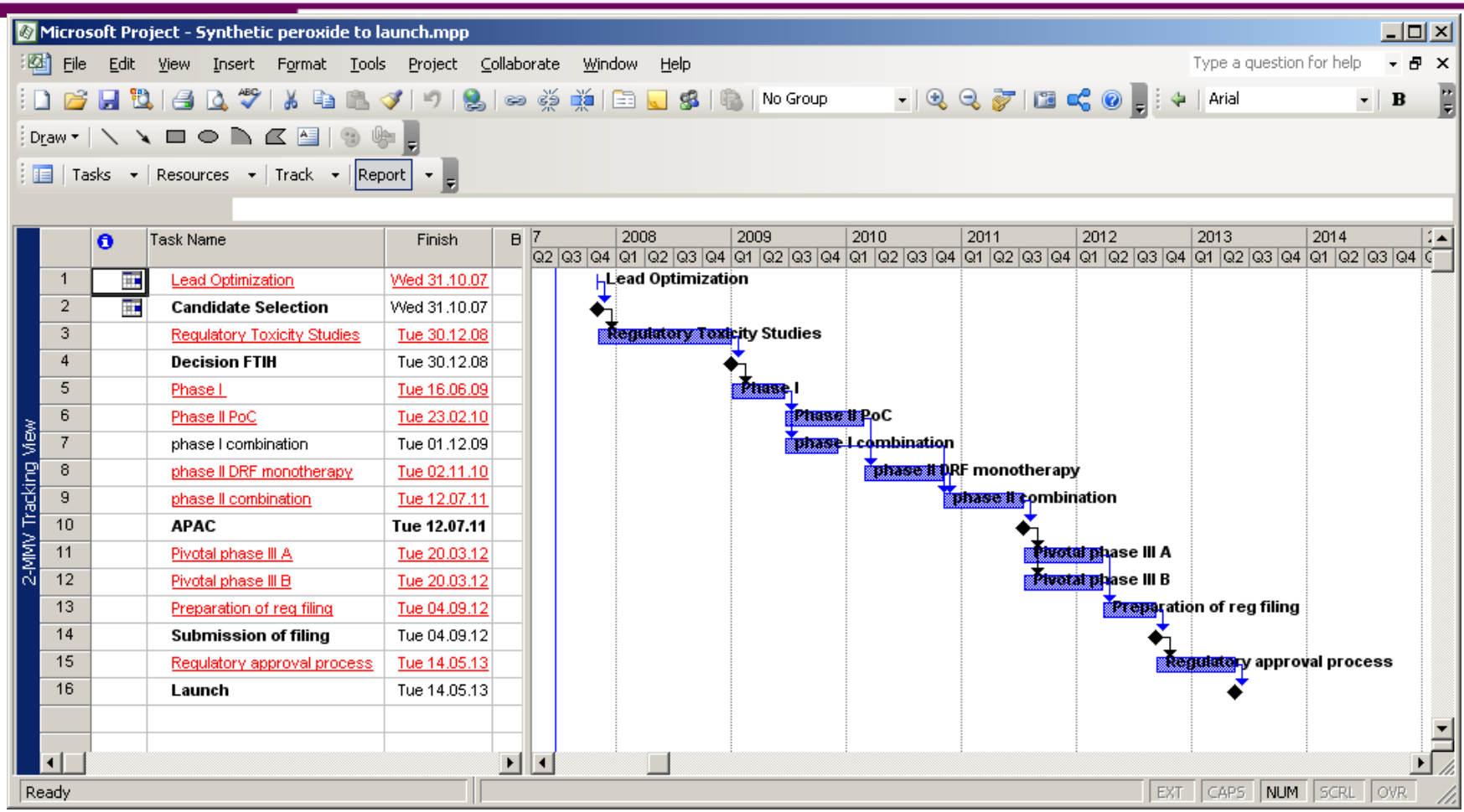
Timelines



Launch → Q4 2013

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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 managment and Consultants**

  Fulcrum, UK, Carl Craft and John Scott, USA

- **Medicines for Malaria Venture**

  Ian Bathurst and Jörg Möhrle

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Thank you

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