Looking to the future: MMV’s discovery and development priorities for malaria eradication

Timothy Wells ScD
Chief Scientific Officer
## Strong pipeline of artemisinin combination therapies

*No ‘one size fits all’ solution*

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Coartem-D</th>
<th>Coarsucam</th>
<th>Eurartesim</th>
<th>Pyramax</th>
<th>AS/MQ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compounds</strong></td>
<td>Artemether</td>
<td>Artesunate</td>
<td>Dihydroartemisin</td>
<td>Artesunate</td>
<td>Artesunate</td>
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<td></td>
<td>Lumefantrine</td>
<td>Amodiaquine</td>
<td>Piperaquine</td>
<td>Pyronaridine</td>
<td>Mefloquine</td>
</tr>
<tr>
<td><strong>75%</strong></td>
<td><strong>25%</strong></td>
<td><strong>25%</strong></td>
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<tr>
<td><strong>Partner</strong></td>
<td>Novartis</td>
<td>sanofi aventis/DND/</td>
<td>sigma-tau/Pfizer</td>
<td>Shin Poong</td>
<td>Farmanguinhos</td>
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<tr>
<td><strong>Launch</strong></td>
<td>1Q’09</td>
<td>4Q’08</td>
<td>4Q’10</td>
<td>1Q’11</td>
<td>2Q’08</td>
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<tr>
<td><strong>Key Selling</strong></td>
<td>Market Leader</td>
<td>First line therapy in</td>
<td>Very long half life</td>
<td>Long half life:</td>
<td>Simple regimen for children and adults</td>
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<tr>
<td><strong>Point</strong></td>
<td>Safety: &gt;250</td>
<td>West Africa</td>
<td>protection at Day 63</td>
<td>protection at Day 42</td>
<td>adults</td>
</tr>
<tr>
<td></td>
<td>million treatments</td>
<td>&gt;20 million</td>
<td>treatments per year</td>
<td>P. vivax clinical data</td>
<td></td>
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<tr>
<td><strong>Paediatric</strong></td>
<td>Dispersible</td>
<td>Dissolves</td>
<td>Crushed tablet</td>
<td>Sachet of</td>
<td>Crushed tablet</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>tablet</td>
<td></td>
<td>Dispersible in 2013</td>
<td>granules in 2012</td>
<td></td>
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</table>
Eurartesim® (dihydroartemisinin/piperaquine)

*The ACT with the longest post treatment protection*

**Partners:** sigma-tau, Pfizer

**Status:**
- Submitted: European Medicines Agency July 09
- Additional studies ongoing – QTc prolongation and PK comparison
- Registration expected 4Q’10

**Future:**
- EDCTP Longitudinal study (3Q’10)
- Paediatric dispersible formulation (2011)
- INESS Implementation study in Mozambique and Burkina Faso (2011)
PYRAMAX® (pyronaridine/artesunate)
First ACT labelled for both P. falciparum and P. vivax

**Partners:** Shin Poong Pharmaceutical, Iowa University

**Status:**
- Submission to the European Medicines Agency (article 58) for tablets (> 15 kg) in May ‘10
- First publication accepted by Lancet

**Future:**
- Drug-drug interaction study (Pyramax-Ritonavir)
- *P. vivax* studies in Papua New Guinea (chloroquine resistant area, 2010), then in Brazil/Peru (2011)
- EDCTP Longitudinal study (3Q’11)
Azithromycin/chloroquine (AZCQ) in IPTp
A new medicine protecting pregnant women

**Partners:** Pfizer, London School of Hygiene and Tropical Medicine

**Rationale:**
- Need therapy Intermittent Preventive Treatment in Pregnancy (IPTp)
- AZCQ safe and efficacious in pregnant women
  - Azithromycin reverses chloroquine resistance
  - Non artemisinin based
  - Antibacterial activity of azithromycin improves maternal STDs

**Status:**
- PK-efficacy: 166 pregnant patients starting Sept’10
- IPTp study in 5000 pregnant women (composite endpoint; live births and low births starts 2011)
OZ439: single dose synthetic peroxide?
*Ready to start phase IIa*

**Background:**
- Second generation synthetic peroxide
- Goal: single-dose cure

**Progress:**
- Completed pre-clinical and phase I in 18 months

**Future:**
- Does it work in patients? 2Q’10
- Does it work in artemisinin resistant malaria? 2011
- Find the best partner for a combination
  - piperaquine, ferroquine, naphthoquine
- Launch planned for 2015
Tafenoquine

*Potential ≤ 3 day radical cure of P. vivax*

**Status:**
- Aiming for ‘better than Primaquine’
  - Shorter treatment, better compliance
  - Safety in G6PD deficient patients
- Clinical safety study in G6PD-deficient patients ongoing in Thailand

**Future:**
- Innovative pivotal phase II/III design (faster and cheaper) – starts Jan ‘11
- Protocol review with US FDA scheduled for Mar ’10

Pre-clinical | Phase I | Phase IIa | Phase II/III | Registration
---|---|---|---|---
2011 | | | | 2015
Preventing relapse of *P. vivax*

New assay formats for testing molecules

- Cell culture assay developed by Dutch Primate Centre using related parasite *P. cynomologi*
  - Validated with known drugs – primaquine, atovaquone
  - Testing 100 key antimalarials in 2010
  - Future: Identifying hypnozoite biomarkers to make better assay
Tools to develop better drugs faster

Designing inhibitors to overcome resistance

• Resistance due to point mutations identified in DHFR

• Structural information used to design new compound P218 which inhibits both normal and mutant DHFR

• Compound entering preclinical development – first time in human 2011

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<tr>
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<th>IC50 (nM)</th>
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<td></td>
<td>Pf sens.</td>
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<tr>
<td>Pyr</td>
<td>58</td>
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<tr>
<td>P218</td>
<td>4.6</td>
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H₂N H₂N

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OH

CO₂H

Pyr: 5-aminolevulinic acid

P218: 6-aminohexanoic acid

Medicines for Malaria Venture
Phenotypic Screening
*Rapidly identifying new classes of antimalarials*

- MMV and partners have tested 5 million compounds against parasite.
- Basis of major collaborations with pharmaceutical companies
- Treasure trove of actives with over 20,000 highly potent starting points
- Moves the drug discovery bottleneck closer to the patient
Hits-to-Leads chemistry

Collaborations to solve the clinical bottleneck

- Hits-to-Leads can be done in house or with dedicated external resource
- Dedicated teams, in disease endemic countries – India, South Africa
- World class industry experts acting as mentors
- *In vivo* pharmacology by centres of excellence
- Partnering with government for training and capacity building
KAE609 Project of the Year
Spiroindolone, a new chemotype for malaria

- Novartis ‘miniportfolio’: consortium, cosponsored with Wellcome Trust
- 2.1 million compounds screened - Spiroindolone scaffold declared ‘lead’ Dec ‘07
- Early pre-clinical studies in 2009
- Excellent drug-like properties
  - Highly bioavailable
  - Highly active - predicted human dose 30 mg
- Active in transmission blocking assays
- First in Man Jan 2011
Priorities for malaria eradication

• Bringing the pipeline to the patient

• Towards the single dose cure

• Collaboration networks bringing exciting new medicines for the eradication agenda
Back-ups
Coartem®-Dispersible (artemether/lumefantrine)
The first ACT designed for children

Partner: Novartis

Status:
• Approved: Swissmedic in Dec ’08, US-FDA ’09
• WHO prequalified
• Registered in 26 African countries, 16 million treatments in ’09

Future:
• Study in asymptomatic subjects to assess community morbidity
  • Expert meeting in March to refine concept
  • Study starts in November ’10
• INESS Implementation study in Tanzania
Coarsucam® (artesunate/amodiaquine)
A model for drug safety monitoring

**Partners:** sanofi aventis, DNDi

**Status:**
- WHO Prequalification Oct ‘08
- Registered in 24 African countries, over 20 million treatments in 2009

**Future:**
- Phase IV program to determine safety and effectiveness in Agboville, Côte d’Ivoire (Nov ’09)
  - Implementation study: open-labeled (15,000 patients) to detect rare adverse events
  - Pre- and post-studies with 290 patients: effectiveness and safety at 2 year-intervals
Research and Development

Strong diverse portfolio for the eradication challenge

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<tr>
<th>Research</th>
<th>Translational</th>
<th>Development</th>
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<tbody>
<tr>
<td>Lead Gen</td>
<td>Preclinical</td>
<td>Phase IIb/III</td>
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<tr>
<td>Novartis miniportfolio</td>
<td>MK 4815 (Merck)</td>
<td>Arterolane/PQP</td>
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<tr>
<td>GSK miniportfolio</td>
<td>GSK 932121 GSK</td>
<td>Eurartesim™</td>
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<tr>
<td>Broad/Genzyme miniportfolio</td>
<td>Iv artesunate Guinil</td>
<td>Pyramax®</td>
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<td>Pfizer</td>
<td>KAE 609 Novartis</td>
<td>AZCO Pfizer</td>
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<tr>
<td>sanofi aventis Orthologue screen</td>
<td>Tafenoquine GSK</td>
<td>Shi P/Université of Iowa</td>
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<tr>
<td>Kinases Monash</td>
<td>P218 DHFR (BIOTEC/Monash/LSHTM)</td>
<td>Coarsucam®</td>
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<tr>
<td>Natural Products 5 Projects</td>
<td>OZ 439 (Monash/UNMC/STI)</td>
<td>sanofi aventis/DND</td>
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<td>Whole Cell Hits St Jude/Rutgers</td>
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<td>Other Projects 13 Projects</td>
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<thead>
<tr>
<th>Lead Opt</th>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Registration</th>
<th>Phase IV</th>
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<tbody>
<tr>
<td>Novartis KAI407 series</td>
<td>GSK 83555 GSK</td>
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<td>GSK Pyridone</td>
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<td>DHODH UTSW/UW/Monash</td>
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<td>Aminooindole Broad/Genzyme</td>
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<td>Ozonide backup Monash/UNMC/STI</td>
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<td>Quinoline Methanols WRAIR</td>
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<td>DHODH Broad/Genzyme</td>
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<td>KAC776 series Novartis</td>
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<td>KA558 series Novartis</td>
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