### Global Portfolio of Antimalarial Medicines

#### Research

<table>
<thead>
<tr>
<th>Lead Optimisation</th>
<th>Project</th>
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<tr>
<td><strong>Oxaboroles</strong></td>
<td>Anacor</td>
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<tr>
<td><strong>DHODH</strong></td>
<td>UTSW/UW/Monash</td>
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<td><strong>OSDD</strong></td>
<td>Univ Sydney</td>
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<tr>
<td><strong>Heterocycles</strong></td>
<td>Dundee</td>
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<tr>
<td><strong>Long Duration</strong></td>
<td>Merck Serono</td>
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<td><strong>HKMT</strong></td>
<td>IC/ CNRS</td>
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<td><strong>dUTPase inhibitors</strong></td>
<td>Medivir</td>
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<td><strong>Imidazolidinediones</strong></td>
<td>WRAIR</td>
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#### Translational

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<th>Phase IIa</th>
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<td>N-tert butyl isouquin Liver STM/GSK</td>
<td>Sarcofucin Methoxyquin Steven Tyler/University of Iowa</td>
</tr>
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<td>AQ13 Immtch</td>
<td>Fosmidomycin Piperaquine Jomes Pharma GmbH</td>
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#### Development

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<tr>
<td>Tafenoquine GSK</td>
<td>Coartem®-D Novartis</td>
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<td>Pyramax Paediatric Farmagaihios/DNDi</td>
<td>Artesunate for injection Guilin</td>
</tr>
<tr>
<td>Eurartesim® Paediatric Sigma-Tau</td>
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<tr>
<td>Artesunate i.r. WHO/TDR</td>
<td>ARCO Naphthoquine/Artemisinin</td>
</tr>
<tr>
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</tr>
<tr>
<td>ASAQ Winthrop sanofi /DNDi</td>
<td>SP-AQ Guilin</td>
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- Included in MMV portfolio post registration
- Non MMV
Global Portfolio of Antimalarial Medicines
Clinical Perspective 2014-2017

Preclinical

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<td>Phase I</td>
<td>Registration</td>
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Included in MMV portfolio post registration

2-3 new clinical candidates per year

New Chemical Entities (mainly)

2017 2015 2014
10% 20% 68%

>90%

Probability

Phase IIb Launch

Non MMV
Global Portfolio of Antimalarial Medicines
Priorities for late stage in Africa

- **Phase IIb/III**
  - Tafenoquine
    - GSK
  - Pyramax Pediatric
    - Shin Poong/University of Iowa
  - Eurartesim® Pediatric
    - Sigma-Tau
  - ArtiMist™
    - Proto Pharma

- **Registration**
  - Mefloquine
  - Artesunate
  - Farmaginhas/WHO/TDR
  - Artesunate i.r.
    - WHO/TDR
  - Arterolane/PQP
    - Ranbaxy
  - ARCO
    - Naphthoquine/Antemisinin

- **Phase IV**
  - Coartem®
    - Novartis
  - Artesunate for injection
    - Guilin
  - Eurartesim®
    - Sigma-Tau
  - Pyramax
    - Shin Poong/University of Iowa
  - ASAQ Winthrop
    - sanofi/DNDi
  - SP-AQ
    - Guilin
Global Portfolio of Antimalarial Medicines
Workstream 1: Making Medicines Available for all

- Safety studies of new ACTs
  - Cardiac
  - Hepatic
- Pediatric FDCs for ACTs
- Pediatric Primaquine (transmission); Tafenoquine (relapse)
- Studies of ACTs in pregnancy
- Studies in co-infection, drug interactions
- Capacity building for these studies in African centres

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</table>
Single dose cure is a priority:
Three day therapy role where ACTs fail

Therapeutic efficacy safely achieved

1. Districts where ACTs have failed
   - **One Day**
     - ✓ High compliance
     - ✓ Directly observed therapy
     - ✓ Low cost of goods
     - ? Need to show activity in artemisinin resistant malaria

2. Districts where ACTs still effective
   - **One Day**
     - ✓ High compliance
     - ✓ Low cost of goods

3. **Three days**
   - ✓ Back-up therapy where ACTs fail
   - ✗ No compliance benefit vs. ACTs
   - ? Cost of goods benefit vs. ACTs

Trade-Off

- ✓ Limited interest to replace ACTs where they are still active
- ✗ No compliance benefit vs. ACTs
- ? Cost of goods benefit vs. ACTs

? Need to show activity in artemisinin resistant malaria
Target Candidate Profiles

1. Fast killers/blood stage
2. Long persisters/blood stage
3a. Relapse prevention,
3b. transmission blocking
4. Chemoprotection

Global Portfolio of Antimalarial Medicines
Workstream 2: Uncomplicated Falciparum Malaria

Preclinical

- P218 DHFR (Biolec/Monash/LSHTM)
- ELQ-300 (USF/OHSU-VAMC)
- 21A092 (DrexelMed/UW)
- MMV390048 (UCT)
- SJ557733 St Jude/Rutgers
- RKA182 Liverpool STM

Translational

- DSM265 (UTSW/UW/Monash)
- Antimalarial Actelion
- CDRI 97-78 Ipca

Development

- OZ439 (Monash/UNMC/STI)
- KAE609 Novartis
- KAF156 Novartis
- Ferroquine Sanofi
- Fosmidomycin Piperaquine Jomaa Pharma GmbH
- Methylene Blue AQ Uni. Heidelberg

Phase I

- KAF156 Novartis

Phase IIa

- OZ439 (Monash/UNMC/STI)
Picking the winners: what capacity do we need

- Safety and Pharmacokinetics preclinically
- Pharmacology platforms
- Formulation development

- In the clinic ‘platform technologies’
  - Safety: cardiology, hepatology in the right populations
  - Drug interactions in the right populations
  - Transmission blocking assays …
  - Ways of assessing drugs for severe malaria: speed and formulation
New preclinical portfolio having eradication fingerprint

Transmission to Human

Liver

Transmission to Mosquito

OZ439
NITD609
GNF-156
ELQ-300
MMV’048
DDD’498
GSK’191

MMV’048
DDD’498

GNF-156
P218
ELQ-300
MMV’048
DDD’498

OZ439
NITD609
GNF-156
ELQ-300
MMV’048
DDD’498

OZ439
NITD609
GNF-156
DSM265
P218
ELQ-300
21A092
MMV’048
DDD’498
SJ’733
GSK’191
Translational portfolio is richer than it has ever been

Most NCEs in translational portfolio have potential against multiple features (1-5 molecules per key feature)
OZ439 trioxalane
Nebraska, STPHI, Monash, MMV

- Fast killer; PRR = 10³-10⁴ /48h
- Time above MPC: potentially >120h
- Transmission blocking
- Mechanism: oxidative > Fe²⁺ mediated radical
- Active against all primary isolates (including Cambodia)
- Phase IIa completed 2012 200mg-1200mg
- Phase IIb with Piperaquine: Protocol submission 4Q’13

Phase II combination
1H 2014
A transformation in drug discovery

- New business model
- Screened five million compounds: 25’000 hits (1 uM)
- Fast: screen to human trials in less than four years
- Seven molecules already in clinical or preclinical
- Identifies previously overlooked new targets

Wells TNC Science 329 1153-1154 (2010)
KAE609 Spiroindolone
Novartis ITD, GNF, STPHI

• Extremely Fast killer; PRR = >10^5 /48h
• Time above MPC: potentially >120h
• Transmission blocking
• Mechanism: PfATP4 – sodium channel
• Active against all primary isolates (including Cambodia)
• Phase IIa first cohorts 2012; second cohorts ongoing
• Phase IIb with 4-aminoquinoline?
• Funded: Wellcome Trust, MMV, now Novartis AG

Phase II combination
2H 2014
KAF156 imidazolopiperazine
Novartis GNF, NITD, BPRC, STPHI

- Fast killer; PRR = $10^4$ /48h
- Time above MPC: >48h
- Active against liver schizonts (chemoprotective)
- Mechanism: PfCARL – unannotated channel
- Active against all primary isolates
- Phase IIa first cohorts 2013
- Funding Wellcome Trust MMV
DSM265 Triazolopyrimididine
UTSW (Dallas), STPHI, Monash

- Medium speed killer; human challenge Nov ‘13
- Time above MPC: > 96h predicted
- Active against liver schizonts
- Mechanism: dihydroxyorotate dehydrogenase
- Active against all primary isolates
- Phase I ongoing
- Phase IIa planned for Peru 2014; Africa phase IIb 2015
- Funding partnership MMV, US NIH

Phase II combination 1H 2015
MMV ‘048 Aminopyrididine
University of Cape Town led

- Medium speed killer? Phase I 1Q’14
- Time above MPC: >96h predicted
- Active against liver schizonts
- Mechanism: novel lipid kinase
- Active against all primary isolates
- Phase I 1Q’14 in Cape Town
- Phase II – Direct to phase II in Africa?
- Funding Partnership MMV, TIA South Africa
P218 2,4-diamino pyrimidine
Biotec Thailand, Monash, MMV

• Medium speed killer?
• Time above MPC: >96h target
• Chemoprotection: pyrimethamine replacement in SMC?
• Mechanism: PfDHFR inhibitor
• Active against all primary isolates, DHFR mutants
• Preclinical
• Phase I 2014? Sporozoite challenge?
• Funding Partnership MMV, Biotec Thailand

Chemo-protection?
Clinical development of combination medicines for uncomplicated falciparum malaria

- Phase I defines safe dose, parasite reduction rate, PK
- (Phase IIa in non-immunes confirms data at high parasitaemia – usually in *P.vivax*)
- Drug interaction studies - in the right population?
- Combination phase IIb studies: 3 doses, different age groups, African children
Partnering strategy in Phase IIb
2013 perspective

New molecule pairs with matched pharmacokinetics and overlapping properties
Partnering strategy in Phase IIb 2013 perspective

New molecule pairs with matched pharmacokinetics and overlapping properties
Partnering strategy in Phase IIb 2014 perspective for EDCTP2

ANThEM: Match the properties of rapidly expanding combinations with the needs of African patients
Managing the risk of attrition

- 3 new clinical candidates per year
- Target convergence PFATP4
  - 21A092 (Drexel) Preclinical; phase I 2014?
  - SJ733 (St Judes) Preclinical; phase I 2015?
- Back-up compounds, de-risking frontrunner
  - MMV’048 follow up; preclinical 2014
  - DSM265 follow up; preclinical 2014
- New classes of molecule
  - DDD498 (Dundee) Preclinical; phase I 2015
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Global Portfolio of Antimalarial Medicines
Workstream 3: transmission blocking

**Translational**

- Preclinical
  - ELQ-300 (USF/OHSU-VAMC)
  - MMV390048 (UCT)

- Phase I
  - KAE609 (Novartis)

- Phase IIa
  - OZ439 (Monash/UNMC/STI)
  - KAF156 (Novartis)
  - Methylene Blue AQ (Uni. Heidelberg)
Global Portfolio of Antimalarial Medicines
Workstream 3: transmission blocking

- All compounds can be registered based on blood schizonticide activity
- EMA/WHO informal feedback
  - Prove concept for blockade of transmission
  - Threshold of parasite free mosquitoes
- Standardized platform for SMFA, DFA
# Global Portfolio of Antimalarial Medicines

## Workstream 4: pregnancy

### Preclinical
- P218 DHFR (Biotec/Monash/LSHTM)
- ELQ-300 (USF/OHSU-VAMC)
- 21A092 (DrexelMed/UW)
- MMV390048 (UCT)
- SJ557733 St Jude/Rutgers

### Translational
- Phase I
  - DSM265 (UTSW/UW/Monash)
- Phase IIa
  - OZ439 (Monash/UNMC/STI)
  - KAE609 Novartis
  - KAF156 Novartis

### Development
- Registration
- Phase IV
  - Coartem®-D Novartis
  - Eurartesim® Sigma-Tau
  - Pyramax Shin Poong/University of Iowa

### Safety Data
- Safety database on ACTs in first trimester, N=600
- Key safety data on differential toxicity for artesunate between rats and humans

### Accelerate standard ICH reproductive toxicity to identify new ‘front runners’
## Global Portfolio of Antimalarial Medicines

### Workstream 5: severe malaria

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- ELQ-300 (USF/OHSU-VAMC)
- 21A092 (DrexelMed/UW)
- MMV390048 (UCT)
- SJ557733 St Jude/Rutgers
- NPC-1161-B University of Mississippi
- RKA182 Liverpool STM

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- CDRI 97-78 Ipca
- DF02 Dilafor
- Ferroquine Sanofi
- Fosmidomycin Piperaquine Jomaa Pharma GmbH
- Methylene Blue AQ Uni. Heidelberg
- SAR97276 Sanofi
- Artemisone UHKST

#### Development
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- Pyramax Paediatric Shin Poong/University of Iowa
- Eurartesim® Paediatric Sigma-Tau
- ARCO Naphthoquine/Artemisinin
- Mefloquine Artesunate Farmagundhos/DNDi
- Artesunate i.r. WHO/TDR
- Arterolane/PQP Ranbaxy
- Eurartesim® Sigma-Tau
- ASAQ Winthrop sanofi/DNDi
- SP-AQ Guillin

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**Note:** The image contains a flowchart that illustrates the pipeline of antimalarial medicines, showing the progression from preclinical to Phase IV development stages.
Global Portfolio of Antimalarial Medicines
Workstream 5: severe malaria

Translational
Preclinical  Phase I  Phase IIa

Development
Phase IIb/III  Registration  Phase IV

OZ439 (Monash/UNMC/STI)
KAE609 (Novartis)
21A092 (DrexelMed/UW)
DF02 (Dilafor)
SAR97276 (Sanofi)
Artemisone (UHKST)

Artesunate i.r. (WHO/TDR)
Artesunate for injection (Guilin)
ArtiMist™ (Proto Pharma)
Global Portfolio of Antimalarial Medicines
Workstream 5: severe malaria

- Target Profile: rapid onset, active against artemisinin insensitive strains
- Formulation: parenteral, sub-lingual (spray?), suppository
- Need standardized testing cascade
- Cast the net wide: piperaquine has a PRR as fast as artesunate.
Suggested priority workstreams for malaria medicines

1. Making medicines safe for all
2. Unparalleled opportunities in uncomplicated malaria
3. Transmission blocking: parallel track with vaccines
4. Picking the winners for pregnancy
5. Severe malaria: parasite reduction platform