Update on drug pipeline and market introduction

CMWG Meeting, Geneva, 6-8th February 2019

Pierre Hugo
MMV Access & Product Management Team

Defeating Malaria Together
What IS MMV?

A foundation of ~80 people working towards the same mission: to reduce the burden of malaria in disease-endemic countries by DISCOVERING, DEVELOPING and DELIVERING new, effective and affordable antimalarial drugs.
We work by operating as a Product Development Partnership (PDP)

With the support of our donors, MMV brings together academic and pharmaceutical partners adding its own scientific expertise to make antimalarial research bear fruit.
We focus on addressing unmet medical needs

RESISTANCE  CHILDREN & PREGNANT WOMEN  SINGLE DOSE CURES  PREVENTION OF RELAPSE  TRANSMISSION BLOCKING  CHEMO PREVENTION
### MMV-supported projects

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<th>Candidate profiling</th>
<th>Preclinical</th>
<th>Human volunteers</th>
<th>Translational</th>
<th>Product development</th>
<th>Patient exploratory</th>
<th>Patient confirmatory</th>
<th>Regulatory review</th>
<th>Access</th>
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<tr>
<td>Miniportfolio GSK</td>
<td>JPC-3210 Janssen</td>
<td>MMV253 ZyduS Cadila</td>
<td>P218 Janssen</td>
<td>Artesunomel/ Ferroquine</td>
<td>Dihydroartemisinin- piperazquin dispersible</td>
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<td>Artesunate for Injection (Galin)</td>
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<td>Phenotypic Lead Daiichi Seriyo</td>
<td>Pantothenates TropiQ/RUME</td>
<td>SAR121 Sanofi</td>
<td>SJ733 Kentucky/Eisai</td>
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<td>Open Source Series University of Sydney</td>
<td>MMV370/71 Janssen</td>
<td>MMV052 Nebraska, Swiss TPI CDCQ</td>
<td>DSM265 Takeda</td>
<td>Cipargamin Novartis</td>
<td>5: Krintafel/Kozenis S. Kant</td>
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<tr>
<td>Phe tRNA ligase &amp; DHODH</td>
<td>MMV048</td>
<td>GS701 GSK</td>
<td>5: ASAQ Winthrop®; 6: SPAQ-CO™; 7: 100mg Artesunate Rectocaps; 8: Artecap™; 9: Krintafel/Kozenis</td>
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<td>Miniporfolio Z Series Novartis</td>
<td>DHODH DTISW/ UW Monash</td>
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<td>SJ733 backup Kentucky</td>
<td>Phenotypic Lead UCT</td>
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<tr>
<td>Plasmepsins UCB</td>
<td>Intra-muscular Galler</td>
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MMV support to projects may include financial, in-kind, and advisory activities.

Footnotes: 1: Included in MMV portfolio after product approval and/or development. DND/ and partners completed development and registration of ASMQ and ASAQ. 2: Global Fund Expert Review Panel (ERP) reviewed product – permitted for time-limited procurement, while regulatory/WHO prequalification review is ongoing. 3: WHO Prequalified OR approved/positive opinion by regulatory bodies who are ICH members/observers. 4: Paediatric formulation.

Brand names: 1: Coartem® Dispersible; 2: Artesun®; 3: Eurartesim®; 4: Pyramax® tablets or granules; 5: ASMQ Winthrop®; 6: SPAQ-CO™; 7: 100mg Artesunate Rectocaps; 8: Artecap™; 9: Krintafel/Kozenis (Trademarks owned or licensed by GSK)
**Coartem® Dispersible**
Novartis
Artemether-lumefantrine for the treatment of children >5kg-<25kg
Approved 2008 SwissMedic; 2012 EMA
Approved in over 50 endemic countries
>350 million treatments distributed

**Eurartesim®**
Alfasigma
Dihydroartemisinin-piperaquine in adults, children and infants >5kg
First stringent approval EMA 2011
Approvals in 20 countries

**Pyramax®**
Shin Poong
Pyronaridine-artesunate for malaria caused by *P. falciparum* or by *P. vivax*
Tablets in adults and children ≥20kg
Granules in children from 5 to <20kg
Positive opinion from EMA (Article 58); new label (tablets) in 2015
Approved in 24 countries
**Artesun®**
Guilin, a Fosun Pharma company

Artesunate for injection
Treatment of severe malaria

**Rectal Artesunate**
Cipla/Strides Pharma

Pre-referral emergency intervention for severe *P. falciparum* malaria in children <6 years and >6h from a treatment centre

**Krintafel/Kozenis (Tafenoquine)**
Trademarks owned or licensed by GSK

Anti-relapse therapy for *P. vivax* malaria
Single-dose 300mg (adult) treatment

WHO prequalification 2010
Approved in 34 countries

Cipla and Strides Pharma WHO
Prequalified in 2018

100mg rectal artesunate included in WHO Essential Medicines List (April 2017 revision)

Approved by US FDA July 2018 and by Australian TGA September 2018
**Artefenomel/FQ**  
(Ex OZ439)  
Sanofi  
MoA:  
• Artefenomel (OZ439): novel, synthetic trioxolane  
• Ferroquine (FQ): inhibition of heme detoxification  

**Lumefantrine/Ganaplacide**  
(Ex KAF156)  
Novartis  
MoA: not yet determined  
Phase IIb combination study ongoing  
Potential for use in severe malaria  
Phase II study completion in 2019/20

**Cipargamin**  
(Ex KAE609)  
Novartis  
MoA: PfATP4 inhibitor  
Potential for use in severe malaria  
Phase II study completion in 2019
**DSM265**

Takeda

MoA: Plasmodial dihydroorotate dehydrogenase (DHODH) inhibitor

Phase IIa in Peru in patients with *P. falciparum* or *P. vivax* malaria completed
Start Phase I combo safety study in 2019

Potential for use in severe malaria
Phase II study completion in 2019/20

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**MMV048**

MoA: PfPI4K inhibitor

Phase IIa in Ethiopia ongoing

Potential for use in severe malaria
Phase II study completion in 2019/20
A key area of focus is the development of child-friendly medicines
Rationale for MFTs strategy

• MFTs strategy: A drug policy with more than one effective treatment for managing uncomplicated malaria cases

• MFTs a promising strategy to extend the useful therapeutic life of the current ACTs (theoretical models) by:
  • reducing drug pressure
  • slowing the spread of resistance

• Scenarios for implementing MFTs:
  • Use of one ACT for CCMm and a different ACT in the clinic
  • Partition of the ACTs market by segment of the same population: paediatric patients, pregnant women, adult patients….
  • Partition of the ACTs market by private/public sectors
  • Mosaic distribution of ACTs: alternative distribution of different ACTs in the same population over a given period of time….
MFTs pilot programme in Burkina Faso

Segmentation of treatment strategy

- Three ACTs will be used in this MFTs pilot programme at the health facility level and each of them will be assigned to a segment of the population as follows:
  - Pyronaridine-Artesunate for children less than five years of age
  - Artemether-Lumefantrin for pregnant women,
  - Dihydroartemisinin-Piperaquine for individuals five years of age and above

- Community case management of malaria: AL given indistinctly to all age categories except pregnant women according to the current recommendations from the NMCP.
SP for IPTp

- **Goal is to bring 2 new QA SP with packaging promoting IPTp**

  1. **Universal (Kenya):**

     - submission of 1st dossier to WHO PQ (Q4)
     - submission to Global Fund ERP (Q4)
     - start countries registration (Q4)

  2. **Manufacturer 1 – Nigeria:**

     - WHO Ethical Review submission of SP bioequivalence (Q2)
     - Contract finalization (Q3)
     - Start of bioequivalence study (Q4)
SEAMACE
(SEASONAL MALARIA CHEMOPREVENTION EXTENSION)

**Improve coverage (3-59 months)**
- Funding Advocacy
- Delivery and implement support

**Age extension (60-120 months)**
- Solidify national interest
- Feasibility & Impact Evidence Gen.
- Analyze SCM and mfg criteria
- Catalyze normative review
- Modelling potential impact of SMC in SE Africa
- Stakeholder Engagement & mapping

**Geographic extension Southern and East Africa**
- Drug repurposing for SE Africa

**Building a path to elimination in seasonal transmission settings**
- SMC PLUS (endecto. and/or trx block)

SMC Continuum
Treatment Landscape: Severe Malaria

Product development

- TDR
- Unitaid
- Cipla

Regulatory approval

- WHO Prequalification
- The Global Fund
- Expert Review Panel

Product readiness

- WHO Standard Treatment Guidelines
- WHO Model list of essential medicines

www.severemalaria.org
Treatment of severe malaria
Rectal artesunate 100mg and Inj AS 60mg

Country adoption & registration

Practice

Improving Access

Inj AS 100Mil vials delivered since WHO PQ ~ 500-600k lives saved

Pre-referral treatment
- 1.5 Mil supp ordered in 2018
- ~180k lives saved

Increasing access to quality assured products for malaria chemoprevention and pre-referral treatment of severe malaria.

Developing innovative approaches to increase rural access to commodities for the case management of severe malaria.

www.severemalaria.org
Sharing best practice:

Our mission: To create an open, accessible knowledge-sharing platform that acts as a repository of information and resources for the severe malaria community and allows the sharing of experiences and best practices in this field of work.

Our vision: A world in which severe malaria case management is significantly improved by freely available information and open access to resources so that no child has to suffer from this fatal disease.
Resources and information

www.severemalaria.org
WHO guidelines were updated in October 2012 to recommend the use of single low dose primaquine for blocking malaria transmission

WHO has conducted a review of the evidence on the safety and effectiveness of primaquine as a gametocytocide of *P. falciparum*, which indicates that a single 0.25mg base/kg is effective in blocking transmission and is unlikely to cause serious toxicity in subjects with any of the G6PD variants. Based on this [WHO] review, the Malaria Policy Advisory Committee (MPAC) recommends the following:

In: (1) areas threatened by artemisinin resistance where single dose primaquine as a gametocytocide for *P. falciparum* malaria is not being implemented, and
(2) elimination areas which have not yet adopted primaquine as a gametocytocide for *P. falciparum* malaria:

A single 0.25 mg base/kg primaquine dose should be given to all patients with parasitologically-confirmed *P. falciparum* malaria on the first day of treatment in addition to an ACT, except for pregnant women and infants <1 year of age.

Single 0.25mg base/kg is **effective transmission blocking agent** and unlikely to cause serious toxicity to G6PD deficient patients

Primaquine potentially has a **major role in reducing transmission** in elimination areas and areas threatened by artemisinin resistance

Single 0.25mg base/kg primaquine dose given to clinically confirmed malaria patients in addition to an ACT
SRA approved Primaquine

<table>
<thead>
<tr>
<th>International Non-proprietary name</th>
<th>Strength/Dose</th>
<th>Dosage form</th>
<th>Supplier/Manufacturer(s)</th>
<th>Global Fund QA Standard</th>
<th>WHO Prequalification/ SRA</th>
<th>Manufacturing site</th>
<th>Country</th>
<th>Material</th>
<th>Pack</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primaquine</td>
<td>7.5mg (as base) (equivalent to 23.2mg Primaquine Phosphate)</td>
<td>Film coated Tablet</td>
<td>Remedica</td>
<td>B</td>
<td>Yes</td>
<td>Limassol</td>
<td>Cyprus</td>
<td>PP/PE/Bottle Al/PVC Blister</td>
<td>100; 1000 10^4 tab, 10^6 100 tab</td>
</tr>
<tr>
<td>Primaquine</td>
<td>15mg (as base) (equivalent to 26.3mg Primaquine Phosphate)</td>
<td>Tablet</td>
<td>Sanofi / Valeant Pharmaceuticals</td>
<td>B</td>
<td>Yes</td>
<td>Laval, Quebec</td>
<td>Canada</td>
<td>HDPE bottle</td>
<td>100</td>
</tr>
</tbody>
</table>

Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification Team: medicines (Published March 2018).

- Primaquine base 3.75 mg tablets
- Primaquine base 7.5 mg scored tablets
- Primaquine base 15 mg tablets
### Combination artemether-lumefantrine primaquine

<table>
<thead>
<tr>
<th>Weight band</th>
<th>Mean weight</th>
<th>Artemether-lumefantrine</th>
<th>Primaquine single dose for 0.25 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-15 kg</td>
<td>10 kg</td>
<td>20 mg/120 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>15-25 kg</td>
<td>20 kg</td>
<td>40 mg/240 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>25 – 35 kg</td>
<td>30 kg</td>
<td>60 mg/360 mg</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>35 kg plus</td>
<td>Based on 40 kg</td>
<td>80 mg/480 mg</td>
<td>10 mg?</td>
</tr>
<tr>
<td>(45 kg plus)</td>
<td>60 kg</td>
<td>80 mg/480 mg</td>
<td>15 mg</td>
</tr>
</tbody>
</table>

Artemether-lumefantrine exposure in >40 kg may be suboptimal:

- Non-immune Columbian and European adults <65kg achieved a cure rate of 100%, while those weighing >65kg achieved a cure rate of 93.4%; all treatment failures were men weighing 69 – 121 kg\(^1\)
- Swedish non-immune patients showed an artemether-lumefantrine cure rate of 100% for those weighing < 65 kg, compared to only 90.4% for those weighing > 65 kg. All failures occurred in adult men of European origin with body weight >65 kg

Further improvements in policy, dosage and availability could accelerate uptake of both LDPQ and PQ for *P. vivax*

1. **Clearly define the therapeutic dose range of SLD PQ for gametocidal clearing of *P. falciparum***
   - Not only will therapeutic dose range inform the development of new, lower strength primaquine tablets, it will also
   - Possible safety concerns of haemolytic effects in G6PDd individuals, as the upper bound of the therapeutic dose range is the highest safe dose in G6PDd individuals

2. **Develop child friendly doses and formulations**
   - Difficult to split the small PQ tablets, that have no “split lines”, limiting confidence that full required dose administered
   - Tablets hard to swallow for young children, also very bitter when crushed and mixed with water. Increase palatability by including sweetened dispersible tablets, as has been developed for AL

3. **Improve packaging**
   - Improve packaging and presentation of primaquine as for Coartem (artemether-lumefantrine) which is marketed as age-targeted blister packs, with pictorial instructions on how it should be taken
   - Include indication for gametocidal clearance for and dose of *P. falciparum*. Currently the label for primaquine lists its indication for the radical cure of *P. vivax* malaria only; dose instructions are for *P. vivax* malaria, and the use of primaquine for *P. falciparum* remains off-label
Tafenoquine update

Defeating Malaria Together

GSK - A catalyst for global health

MMV - Medicines for Malaria Venture
The tafenoquine (TQ) proposition: G6PD testing + single dose radical cure

Quantitative G6PD diagnostic test

Tafenoquine single dose
P. vivax: aspiration for tomorrow…

**DECISION TOOL**

- **G6PD** quantitative test

- **PRIMAQUINE**
  - **3 DAY** Blood-stage
  - **7-14 DAY** Liver-stage

- **TAFENOQUINE**
  - **3 DAY** Blood-stage
  - **1 DAY** Liver-stage

Improving *P. vivax* outcomes
TQ approved by the US FDA and TGA; submission in malaria endemic countries on-going

• Approved by the US FDA on 20th of July
• Approved by the Australian TGA on 12th of September
• Submitted for regulatory approval in Brazil on 4th of September
• Actively preparing MAA submissions for Peru, India, Ethiopia, Vietnam, Thailand & Colombia
Overall objectives of the feasibility studies planned in Brazil, Thailand and Ethiopia

• Assess operational feasibility and safety of appropriate radical cure after G6PD testing under field conditions

• How to scale-up?
  Define core package of supporting interventions for scaling-up (Training, supervision, surveillance, pharmacovigilance)
THANK YOU to our committed funders