Improving case management of uncomplicated malaria

Increasing treatment options for children with uncomplicated malaria

There are still relatively few child-friendly antimalarial formulations available today. As a result, many children still receive adult formulations – usually tablets that need to be crushed, and which taste bitter, causing children to either refuse the medicine or vomit on administration. This can lead to under-dosing, resulting in incomplete cure, which in turn can promote drug resistance.

MMV and partners have prioritized the discovery, development and delivery of new and effective antimalarial drugs for children. In February 2009, MMV and Novartis launched Coartem® Dispersible (artemether-lumefantrine), the first ever high-quality artemisinin-based combination therapy (ACT) developed especially for children. As of year-end 2018, 385 million treatment courses had been provided to vulnerable children suffering from malaria – a volume that MMV estimates to have saved around 825,000 lives.

The second child-friendly ACT to emerge from MMV’s pipeline was a granule formulation of Pyramax® (pyronaridine–artesunate), which was granted a positive scientific opinion by the European Medicines Agency (EMA) in 2015. Co-developed by MMV and Shin Poong Pharmaceutical, Pyramax granules are now included on the World Health Organization (WHO)’s List of Prequalified Medicinal Products and Essential Medicines List (EML) for children (EMLc).

Approval of a third child-friendly ACT is anticipated in 2019. MMV’s partner Alfasigma S.p.A. is preparing to submit a data package to the EMA for a paediatric re-formulation of Eurartesim®(dihydroartemisinin–piperazine), an existing ACT approved in tablet formulation for the treatment of uncomplicated malaria. If approved, Eurartesim paediatric will increase child-friendly treatment options for endemic countries, thereby helping to improve case management.

As of year-end 2018, Coartem Dispersible was registered in 31 African countries and Pyramax granules in 13 African countries. MMV will continue to work with its partners throughout 2019 to support further roll-out of these drugs.

References:
1. Estimates calculated by MMV based on initial lives saved data with inputs from 2012–2016 malaria indicator surveys.
2. Pyramax® tablets for adults were first approved by the EMA in 2012.
3. Under its Article 58 procedure, the EMA (in cooperation with the WHO) can provide scientific opinions on high-priority medicines intended exclusively for markets outside of the European Union, thereby facilitating patient access to essential medicines in low- and middle-income countries.
4. Set up in 2001, the WHO’s prequalification programme is designed to “facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis.”
5. The WHO EML lists the “minimum medicine needs for a basic healthcare system, listing the most efficacious, safe and cost-effective medicines for priority conditions.” The latest (20th) edition of the EML for adults, and the latest (6th) edition of the EML for children, were both published in 2017.
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Revised text:

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Millicent’s story

Millicent is from Kisumu, a port city on the banks of Lake Victoria in Kenya. The lake is a rich breeding ground for mosquitoes and so malaria thrives. Millicent suffered severe malaria and nearly died when she was just 1 year old. Fortunately, she was able to access appropriate treatment including the first high-quality paediatric ACT (artemether-lumefantrine).

The name Millicent means “strong at work” and she lives up to it. Today, aged 10, Millicent is hard working and successful at school and enjoys life. Her family is thankful for those who developed the child-friendly treatment.

Expanding access to ACTs with real-world studies

To support optimal use of all available ACTs, MMV is working with partners to generate post-approval evidence of their effectiveness, tolerability and safety in the real world.

One such study is the Phase IIIb/IV CANTAM study, which is gathering data on the use of Pyramax in treating 8,572 malaria episodes in adults and children across five endemic countries in sub-Saharan Africa. It is hoped that data from this study will support the roll-out of Pyramax in a wider range of patients, including those with co-infections and abnormal liver function, as well as in very young children (<1 year of age), and children who are malnourished. Completion of enrolment is expected in the first quarter of 2019.

Another novel post-approval study involving Pyramax is underway in Zambia and The Gambia. This study is exploring the efficacy of different dosing regimens of Pyramax in clearing parasites in individuals who are infected with Plasmodium falciparum, but are asymptomatic (i.e. show no clinical symptoms of the disease yet remain an important reservoir for transmission). Enrolment is expected to be complete in the first quarter of 2019. Positive results from this study may inform future approaches for community-wide treatment campaigns in which asymptomatic carriers represent a large portion of the target treatment group.

8. Pyramax granules are currently approved for the treatment of children weighing 5–20 kg, meaning that children under 5 kg are not eligible to receive the drug.
3. Improving case management of uncomplicated malaria

### Developing next-generation cures

ACTs are currently the cornerstone of treatment for uncomplicated malaria. However, two factors threaten their effectiveness: artemisinin resistance,9 which emerged in the Greater Mekong sub-region a decade ago, and the potential for non-compliance to treatment. ACTs are administered over 3 days, meaning it is never guaranteed that patients will complete their treatment course, especially if they start to feel better before the end. Non-completion of treatment can then also contribute to the development of resistance.

New treatments that are not based on artemisinin are urgently needed. A new treatment should quickly clear all parasites, including resistant strains, from the blood, and have a simple dosing regimen and a good safety/tolerability profile. It would also have the potential to block the transmission of parasites from humans back into mosquitoes, prevent relapsing malaria (caused by *Plasmodium vivax* and *Plasmodium ovale*), and provide post-treatment prophylaxis.10 The ideal treatment would be a single-exposure radical cure (SERC), which would transform the case management of malaria and strongly support population-wide elimination efforts.

#### Table 1: Activity of MMV-supported molecules in development, 2018

<table>
<thead>
<tr>
<th>Target indication</th>
<th>Partner (former partner)</th>
<th>Stage of development</th>
<th>Asexual blood-stage activity</th>
<th>Potential to block transmission</th>
<th>Potential to prevent relapse</th>
<th>Potential for prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artefenomel (OZ439)/ferroquine (FQ)</td>
<td>Sanofi (Monash Univ./Univ. of Nebraska/Swiss TPH)</td>
<td>Patient exploratory</td>
<td>(Phase IIIb)</td>
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<tr>
<td>Ganaplacide (KAF156)/lumefantrine</td>
<td>Novartis</td>
<td>Patient exploratory</td>
<td>(Phase IIIb)</td>
<td></td>
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<tr>
<td>Cipargamin (KAE609)</td>
<td>Novartis</td>
<td>Patient exploratory</td>
<td>(Phase IIIa)</td>
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<tr>
<td>DSM265</td>
<td>Takeda ([Univ. of Texas Southwestern]/Univ. of Washington/Monash Univ.)</td>
<td>Patient exploratory</td>
<td>(Phase IIIa)</td>
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<tr>
<td>MMV048</td>
<td>([Univ. of Cape Town])</td>
<td>Patient exploratory</td>
<td>(Phase IIIa)</td>
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<td></td>
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<tr>
<td>M5717 (DDD498)</td>
<td>Merck KGaA ([Univ. of Dundee])</td>
<td>Phase I</td>
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<tr>
<td>P218</td>
<td>Janssen (Biotec Thailand)</td>
<td>Phase I</td>
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<tr>
<td>MMV253</td>
<td>Zydus Cadila (AstraZeneca)</td>
<td>Phase I</td>
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<tr>
<td>MMV533 (SAR441121)</td>
<td>Sanofi/MMV</td>
<td>Phase I</td>
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<tr>
<td>MMV370/MMV371</td>
<td>Janssen (Calibr)</td>
<td>Preclinical</td>
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<tr>
<td>MMV052</td>
<td>MMV (Univ. of Nebraska, Swiss TPH, CDCO)</td>
<td>Preclinical</td>
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</tbody>
</table>

9. Resistance to artemisinin can in turn lead to resistance to the partner drug.
10. A prophylactic drug kills the liver-stage (sporozoite) form of the malaria parasite, thereby halting the parasite lifecycle and preventing a subsequent blood-stage infection from taking hold.

CDCO: Centre for Drug Candidate Optimisation, Monash University, Melbourne, Australia; Swiss TPH: Swiss Tropical and Public Health Institute
Artefenomel (OZ439)/ferroquine (FQ)

One approach to achieving such a next-generation cure is to combine a novel, fast-acting compound with a longer-acting compound. Artefenomel/FQ, currently under development by MMV and Sanofi, is one example of this approach.

Artefenomel is a fast-acting agent that quickly kills most parasites in the blood and alleviates the clinical symptoms of malaria within a short timeframe, while FQ is a longer-acting agent that destroys any remaining parasites. As a single-dose treatment, artefenomel/FQ has the potential to reduce dosing frequency by a third (compared with the currently available ACTs), thereby improving patient compliance and, crucially, slowing down the development of resistance.

Artefenomel/FQ is currently being tested in a Phase IIb combination study. This Phase IIb trial is underway to determine the efficacy and safety of a single dose of artefenomel/FQ in patients aged 6 months to 14 years, as well as the optimal dose. As of the end of 2018, a total of 165 patients were enrolled in the trial. Interim results are expected in the first quarter of 2020.

In parallel, MMV and its partners are also conducting a separate Phase IIa study to satisfy the US Food and Drug Administration (FDA)’s “combination rule”. In this study, varying doses of artefenomel are being studied in combination with a constant dose of FQ. The study began in September 2018 and the last patient last visit is scheduled to occur in 2019.

In 2019, MMV will take over operational responsibility for the Phase II trials from our partner, Sanofi. MMV will work to optimize recruitment at participating trial sites, as well as plan further studies to assess the tolerability and palatability of a milk powder formulation in children.

Artefenomel is a fast-acting agent that quickly kills most parasites in the blood.
Ganaplacide (KAF156)/lumefantrine

A second novel combination, ganaplacide (KAF156)/lumefantrine, is currently being assessed for its potential use as a SERC. The new solid dispersion formulation of lumefantrine (lumefantrine-SDF) allows once daily treatment. It is hoped that the complementary activity of ganaplacide and lumefantrine-SDF will enable the simplification of treatment.

In 2017, MMV and Novartis initiated a Phase IIb clinical trial of ganaplacide/lumefantrine-SDF in Africa and Asia. The trial is looking at a 3-day treatment regimen, but also at simplification to two doses and a single dose, both of which have the potential to improve patient compliance and cure drug-resistant strains of malaria.

Why is ganaplacide/lumefantrine an exciting combination?

► Ganaplacide (KAF156) is a fast-acting compound with a novel mechanism of action, capable of killing both *P. falciparum* and *P. vivax* parasites. It is active against parasites that are resistant to the currently used antimalarial drugs and stays in the blood for up to 10 days. Its partner lumefantrine is a new, single-dose formulation of a registered compound. As a long-acting agent, lumefantrine stays in the blood for up to 28 days, clearing any remaining parasites. The combination also has the potential to prevent malaria infections taking hold and to block transmission of the disease.

How is the Phase IIb trial progressing?

► The trial is currently active in seven African countries and two Asian countries. Between November 2017 and October 2018, we successfully recruited 337 patients aged 12 years and above. We are currently analysing the data from this group, with a view to starting the second phase of the study in patients aged 2–12 years in May 2019. Our recruitment target for this next phase is 175 patients, which we hope to achieve by November 2019.

What are the benefits and challenges of running clinical trials in Africa?

► The main benefit is the opportunity to study new drug combinations in patients who live in malaria-endemic countries. It also allows us to engage with local principal investigators who are not normally involved in conducting clinical trials, which helps to support local research capacity in the communities worst impacted by malaria. There can be logistical challenges, such as transporting medicinal products to, or collecting samples from, remote rural sites, but on this project we have worked closely with each country to ensure that local infrastructure is in place to support the trial and that the staff involved have been adequately trained.

What impact could ganaplacide/lumefantrine have on the treatment of malaria?

► If approved as a single-dose cure, ganaplacide/lumefantrine would be a very important addition to current treatment options for malaria. We know that patient compliance to treatment remains an issue, not just with malaria but in other diseases, so if we could give a full curative dose in just a single treatment, it would greatly improve outcomes and go a long way towards supporting malaria elimination efforts.

What has it been like to work with MMV on this project?

► MMV has lots of experience in bringing together multiple sponsors and partners to develop the next generation of antimalarial medicines. On this project, we have benefited greatly from MMV’s support, advice and knowledge sharing. Collaboration in global health is vitally important because knowledge lies in so many different places. If we can tap into each other’s knowledge and expertise, as we have on this project, I believe we will achieve our goals.
Cipargamin (KAE609)

Cipargamin (KAE609) is also undergoing Phase II testing. The compound offers the dual possibility of becoming part of a SERC or a next-generation treatment for severe malaria.

The sodium channel in the parasite targeted by cipargamin (PfATP4) is the first validated new molecular target for malaria in more than 20 years. In a Phase IIa proof-of-concept study in Thailand, cipargamin rapidly cleared parasites from the blood of adults with uncomplicated *P. falciparum* or *P. vivax* malaria. A subsequent study showed the compound’s good longevity in the blood, with a 75 mg dose staying above the concentration needed to kill parasites for over 8 days. In addition to its asexual blood-stage activity, cipargamin has shown the potential to block transmission of malaria.

To further characterize the safety profile of cipargamin, the compound is undergoing a Phase IIa safety study with last patient last visit expected by May 2020.

In pursuit of a next-generation treatment for severe malaria, an intravenous (IV) formulation of cipargamin underwent toxicology and preclinical safety assessments in 2018. A first-in-human study using the IV formulation is estimated to start in the third quarter of 2019.

Novartis is developing cipargamin in collaboration with MMV with financial and technical support from Wellcome Trust.

15 Standard membrane feeding assay.
16 Cipargamin was originally discovered as part of a Novartis-led consortium, funded by MMV, Wellcome Trust and the Singapore Economic Development Board in collaboration with the Swiss Tropical and Public Health Institute.
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Maintaining a healthy pipeline of candidate antimalarial drugs

The two current combinations undergoing Phase IIb testing, artefenomel/FQ and ganaplacide/lumefantrine-SDF, are still some distance from registration. Based on the industry average, each has less than a 50% chance of becoming an approved product. To balance the risk of failure that is inherent to drug development, there is a need to maintain a healthy pipeline, and to ensure a steady flow of new candidates into clinical development.

A healthy pipeline is important for three main reasons. Firstly, clinical compounds and combinations can fail at any stage of development for reasons of safety, tolerability or efficacy. Secondly, because MMV’s strategy sets out the need for a wide range of target candidate and target product profiles, delivering a high diversity of compounds is essential. Finally, even in the post-approval setting, medicines remain at risk of failure because of resistance in the field.

In 2018, several of MMV’s portfolio compounds progressed in their early clinical and preclinical testing.

**M5717**

M5717 (formerly DDD498), in development with Merck KGaA, is the first compound in the portfolio to have shown comparable activity across all stages of the parasite lifecycle (except for the dormant liver stage of *P. vivax* malaria), as well as prophylactic activity. In 2018, single, ascending doses of M5717 were evaluated in a Phase I study, and the compound was shown to be safe and well tolerated. The challenge now is to find the ideal combination partner. Using the SCID model, M5717 has been studied in combination with several of MMV’s priority compounds, with several other combination studies initiated. After completion of the Phase I study, the next stage will be to select the best combination partner and to start combination studies in humans.

**MMV253**

Originally discovered in India as part of MMV’s collaboration with AstraZeneca in Bangalore, MMV253 is now being developed by Zydus Cadila, an Indian Pharmaceutical company. In preclinical studies, MMV253 has shown an ability to rapidly clear parasites, has a long presence in the blood after a single dose, and a good safety and tolerability profile. The compound also appears to have a new mechanism of action.

In 2018, MMV and Zydus Cadila completed manufacturing, toxicology and GLP-compliant safety studies, supporting the decision to progress MMV253 to Phase I clinical trials – scheduled to start in early 2019.

"The Zydus-MMV collaboration is based on alignment of our philosophy of creating healthier communities globally. Zydus is strongly committed to the discovery and development of novel and affordable therapies. MMV brings disease-specific expertise in malaria drug development and has access to a large network of clinical sites. The efforts by MMV towards the eradication of malaria globally are truly commendable. Together, Zydus and MMV will work to develop MMV253 as a potential next-generation antimalarial."
MMV533

MMV533 (also known as SAR441121), in development with Sanofi, has shown rapid in vitro and in vivo parasite clearance activity, as well as a low predicted dose and a long predicted half-life in humans. As such, MMV533 has the key characteristics of a potent, long-acting treatment. In addition, laboratory experiments specifically designed to generate resistance to MMV533 in malaria parasites have been unable to do so.

In 2018, MMV and Sanofi successfully completed preclinical safety and toxicology studies, and the compound has now been approved by MMV’s Global Safety Board for testing in human volunteers.

New drug candidates

In 2018, MMV’s Expert Scientific Advisory Committee20 recommended three new candidates for progression to preclinical testing: a new endoperoxide, MMV052;21 a novel compound from GSK, GSK701;22 and two prodrugs23 of atovaquone for use in a potential injectable prophylactic drug (MMV370/MMV371; with a view to selecting one during preclinical safety studies).

Behind these, there are currently over 30 different chemical series being worked on by MMV and its partners, with a view to approving two new preclinical candidates each year from the studies that MMV finances. In addition, MMV envisages that one new preclinical candidate each year will come from projects for which MMV is providing advice, but not direct funding.

20 Expert Scientific Advisory Committee: an external body of experts that helps to identify the best projects worthy of inclusion in MMV’s portfolio and continues to monitor progress through an annual review of all projects.
21 Now undergoing GLP toxicology studies.
22 GSK-owned compound being developed by GSK.
23 Prodrug: a precursor of a drug that must undergo chemical conversion by metabolic processes in the body before becoming an active pharmacological agent.