Developing
next-generation antimalarials

Simplifying malaria case management with novel therapies

ISSUES
To stem the emergence of malaria drug resistance, the WHO recommends the use of a combination of drugs that act in different ways. The current artemisinin-based combination therapies (ACTs) must be taken once or twice daily over a period of 3 days. Several studies have shown that patients often do not adhere to, or complete, the recommended regimen, which can lead to the emergence of drug-resistant parasites. ¹

Multidrug-resistant malaria has already emerged in the Greater Mekong Sub-region of Southeast Asia, resulting in high levels of treatment failure.² Current short-term efforts to manage drug-resistant infections involve the use of longer treatment courses and studies are ongoing to explore the use of triple combinations. In the longer term, new medicines with novel mechanisms of action are needed to ensure malaria can continue to be cured in the face of increasing drug resistance.

ACTION
MMV prioritizes the development of new therapies with novel mechanisms of action, activity against all known resistant parasite strains and more convenient treatment regimens.

Within MMV’s portfolio, two new combinations have reached phase IIb development – artefenomel/ferroquine and KAF156/lumefantrine. Both of these combinations have the potential to meet this target and both are being tested against all known multidrug-resistant malaria parasites. It is hoped these new drug combinations will one day be at the front line of antimalarial treatment. A summary of the biological activities related to MMV-supported molecules in development including these two drug combinations is provided in the adjacent table.

As with the current ACTs, future medicines should be based on a combination of two or more compounds. MMV and its partners are undertaking non-clinical, combination studies earlier in the drug development pathway than has historically been the case. These studies are providing information on the compatibility of candidate compounds and predictions on their dose and efficacy as partner molecules (see pp. 38–39). Together with our drug discovery work, this extensive, ongoing R&D effort ensures that MMV’s antimalarial drug pipeline continues to be replenished. What follows in this chapter is an update of seven of our more advanced antimalarial drug projects.

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SERC: single-encounter radical cure; Swiss TPH: Swiss Tropical and Public Health Institute
If full resistance develops and spreads... then we will consider modifying our programme as quickly as possible to make the drug available in areas where resistance has emerged.
KAF156/lumefantrine

KAF156 is the first compound to progress into clinical development from the novel imidazolopiperazine class of antimalarial molecules. A key strength of the drug is its potential to both treat and prevent malaria, including resistant strains.

Phase IIa studies have demonstrated that KAF156 rapidly kills both *P. vivax* and *P. falciparum* malaria parasites. In 2017, Novartis, in partnership with MMV, initiated a phase IIb study to evaluate the combination of KAF156 plus a new formulation of lumefantrine.

What advantages does this new combination have over current treatment?

The first advantage of this combination is its activity in drug-resistant parasites. This was demonstrated preclinically and then in our proof-of-concept study, where we saw many patients who were infected with strains of parasites that possessed markers of resistance or reduced sensitivity to artemisinin. KAF156 monotherapy was able to clear these parasites from the patients.

The phase IIb study is investigating KAF156 in combination with a new formulation of lumefantrine. The combination is currently being evaluated as a single dose, administered for 1, 2 and 3 days. At the moment, it holds great potential in being effective as a one-day regimen. Compared with today’s treatment options, the KAF156/lumefantrine combination’s easier dosing schedule could increase patient compliance, and subsequently reduce the emergence of resistance.

What are the phase IIb study objectives?

The overarching objectives are to characterize the activity, efficacy and toxicity of the combination of KAF156 and lumefantrine. The dosage and ratio of the partner drugs, as well as duration of therapy, are being evaluated in adults, children and infants, all in one complex study. We are looking for a therapy that is adapted to children’s needs, with the shortest possible treatment regimen. We will then take this forward into phase III studies.

How might these considerations change should we see an increase in artemisinin drug-resistance?

The global community is actively monitoring for artemisinin resistance. So far, no confirmed cases have been detected in Africa, but we are seeing cases of delayed parasite clearance in Asia. If full resistance develops and spreads, as we’ve seen with other antimalarial treatments in the past, then we will consider modifying our programme as quickly as possible to make the drug available in areas where resistance has emerged. We will of course be following recommendations from regulatory authorities to ensure we are doing the right thing for patients.

How is the phase IIb programme progressing?

Despite the trial complexity, the phase IIb study is progressing very well. It is being run in various sites across nine countries – seven in Africa and two in Asia. A run-in cohort of 12 patients was completed in September 2017, and as of March 2018, more than 100 adults and adolescents have been enrolled in Part A of the study. We expect to complete the interim analysis in early 2019 and then quickly move to Part B, which will evaluate the optimized drug combinations and treatment durations in patients aged 2–12 years.

What do each of the partners bring to the table?

The partnership between Novartis and MMV has been great! There is tremendous wisdom and power within the team, bringing a wide range of experience and diversity in terms of the overall strategy and design of the studies. MMV is able to anticipate the operational challenges we might face through their prior experience with other partners and running studies in malaria-endemic countries. Together with the interests and legacy of Novartis in this field, we can put together the best people on the project, who are experienced and motivated.

What are Novartis’ future priorities in antimalarial drug development?

Our priority will be to continue to advance research for new active antimarials, especially against resistant strains, to secure the gains made in the fight against malaria and progress toward elimination. We will also be focusing on drugs that block malaria transmission by targeting drug candidates that are active against gametocytes. Our aim is to ensure our new medicines are designed to benefit the populations with the greatest disease burden and needs: women who are pregnant or with child-bearing potential, and children. Developing medicines that are ‘friendly’ to these vulnerable populations is a high priority, as is including these populations in our trials as early as we can.
The combination of artefenomel (formerly known as OZ439) and ferroquine (FQ) has the potential to become the first of a new generation of antimalarials not based on artemisinin and therefore an important tool in the context of drug resistance. MMV and Sanofi are currently conducting a phase IIb programme to determine the safety and efficacy of the combination as a single-dose cure.

**What is exciting about the artefenomel/FQ combination?**

Artefenomel/FQ represents a novel class of drug with no apparent cross-resistance to existing treatments, meaning it has the potential to treat patients affected by drug-resistant parasites. It also has the potential to reduce dosing frequency, thereby improving adherence to treatment and preventing the emergence of further drug-resistant strains of parasite.

**What are the challenges of developing an effective single/multiple-exposure radical cure?**

Formulation is the key challenge to achieving a simplified therapy, either as a single or multiple dose, as it must be adapted for a range of patients, including those who are very young or very ill. Among others, a formulation that includes powdered milk to simulate food is under investigation. MMV has also worked with Sanofi and other manufacturing experts to resolve challenges in manufacturing quality and move the project forward.

**What does the phase IIb programme involve? When will the results be available?**

The programme includes two mirrored dose-finding studies: the first combines varying doses of FQ with a fixed dose of artefenomel; the second combines varying doses of artefenomel with a fixed dose of FQ. Results are expected in 2019.

**Can you explain how this reduced-dose cure will work?**

The treatment combines a potent, fast-acting agent (artefenomel) that can kill most parasites in the blood and quickly decrease the symptoms of malaria, with a long-lasting agent that clears the remaining parasites (FQ).

**For a pharmaceutical company such as Sanofi, what are the advantages of partnering with MMV on this project?**

MMV is a great organization with a lot of know-how in the field of malaria and antimalarial drug development. It is smaller and leaner than Sanofi, allowing for more flexibility. Partnership is vital to share the risks of development for tropical or neglected diseases; our partnership is a good model, and I highly value our collaboration on a personal and organizational level.
DSM265

DSM265 is one of the new generation of novel antimalarials and has the potential to both treat patients and protect healthy people with a reduced dosing schedule. It also has the potential to address resistance to current treatments. The compound was discovered in partnership with the University of Texas Southwestern (USA), Washington University (USA) and Monash University (Australia), and has since demonstrated safety and efficacy against Plasmodium falciparum in a phase IIA trial in Peru. DSM265 is being developed with the support of Takeda Pharmaceutical Company Ltd (Japan). DSM265 was the first compound to be studied in sporozoite volunteer infection studies (VIS), (previously known as the controlled human malaria infection model).

What is exciting about DSM265?

A single dose of DSM265 typically clears blood stages of *P. falciparum* parasites within 48 hours, which is very impressive. It works by targeting an essential enzyme in the malaria parasite (dihydroorotate dehydrogenase, DHODH), which is required to make parasite DNA and RNA. Data from cellular models showed that the compound could block replication of the parasite in human liver cells as well as red blood cells; it should therefore be able to both stop and treat blood-stage infection. On this basis, we decided to test DSM265 in a sporozoite VIS.

What is special about the sporozoite VIS platform? How will it be used in the future?

Our approach to these studies comes from the lessons learned in volunteer studies with blood-stage malaria. VIS is a good platform with which to compare new molecules since the studies can be done using a small number of volunteers, and early in clinical development. The key difference between sporozoite VIS and blood-stage VIS is that the former assesses a drug’s ability to protect against infection getting into the bloodstream, whereas the latter is used to assess a drug’s ability to treat infection once it is already established in the bloodstream.

DSM265 was the first compound to be investigated in the sporozoite VIS platform. This study confirmed the chemoprotective activity of one dose of DSM265 given a week before infection. This result was published in *The Lancet Infectious Diseases* in March 2017.¹ All of MMV’s pipeline drugs with similar properties can now be put through this platform to test their chemoprotective potential.

What are the next steps?

This DSM265 study helped validate the sporozoite VIS platform, which can now be used for other compounds with liver-stage activity, such as P218 (p. 37).

The next steps for DSM265 include confirmatory work on a new therapeutic formulation, and completion of planned combination studies to find a suitable partner. It is still early days, so the final partner drug for DSM265 has not yet been selected. The other question is whether to prioritize its treatment indication, or whether to push forward with its development as a medicine to protect people at risk of infection.  

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M5717 (formerly DDD498)

M5717 was identified through a collaboration between MMV and the Drug Discovery Unit, University of Dundee, Scotland. It is a compound with a novel mechanism of action, targeting the protein-making machinery of the malaria parasite. The compound has demonstrated activity against all stages of the malaria parasite’s lifecycle and thus has the potential both to treat and to protect vulnerable populations. M5717 is being developed in partnership with Merck KGaA.

Merck has included volunteer infection studies (VIS, see p. 29) in their M5717 development programme, representing the first time VIS have been conducted by a pharmaceutical company as part of phase I. The goal of the studies is to understand the drug’s efficacy against the blood stage of the malaria parasite’s lifecycle earlier than previously possible. M5717 was also tested in combination with other compounds from the MMV portfolio in a mouse model of human malaria, to enable the selection of combination partners for further development (see pp. 38-39).

What is exciting about M5717 as a potential antimalarial?

Preclinical studies have shown M5717 is active against all stages of the malaria lifecycle and is long acting. This unique profile suggests an important role in the future treatment of malaria. We are very excited about the initial data, and hope that the compound will live up to our expectations during clinical development.

What led to Merck partnering with MMV?

It started with Merck’s interest in neglected tropical diseases – especially schistosomiasis – and some early research in the field of malaria. These elements came together with the creation of the Merck Global Health Institute, which is dedicated to developing health solutions for the most vulnerable populations in developing countries.

Malaria is still one of the top killers of children, so we urgently need new antimalarials. Partnering with MMV allows us to benefit from their malaria expertise and gives MMV access to our R&D expertise, helping to ensure our joint programmes move forward.

How are the phase I trials progressing, and what is the role of the VIS platform?

We started the first-in-human (FIH) phase I study in September 2017; this included a VIS in Brisbane, Australia. FIH phase I trials are ‘business as usual’, but the VIS platform is a new area for us. We hope it will provide us with an early understanding of drug efficacy, which will guide the design of our phase II trials. It’s about finding ways to reduce timelines, manage resources and minimize the number of patients needed in the trials.

Initial data are promising, and step by step we will see if all the expectations we have for this compound are realized.

Dr Jutta Reinhard-Rupp
Head of Merck Global Health Institute, Merck Group, talks about the vision of the Merck Global Health Institute, its partnership with MMV, and how volunteer infection studies (VIS) are contributing to the clinical evaluation of M5717.

“Malaria is still one of the top killers of children, so we urgently need new antimalarials.”
**MMV048**

MMV048 is a novel antimalarial that works by inhibiting the parasite enzyme phosphoinositol 4-kinase and has good activity against both liver and erythrocytic schizonts (the maturing cells in the liver and blood, and the dividing cells in the blood). The compound was discovered and researched by an international team led by Prof. Kelly Chibale from the University of Cape Town, South Africa, and was the first potential antimalarial medicine to enter a first-in-human (FiH) phase I study in Africa. In volunteer infection studies it showed good activity at very low doses, making it one of the most potent compounds in the portfolio.

Following completion of the FiH study, MMV progressed MMV048 to a study in malaria patients (phase IIa) in Ethiopia. Ethiopia was chosen owing to the presence of both *Plasmodium falciparum* and *Plasmodium vivax* malaria, thereby allowing the compound's activity to be assessed in both of these two main species of malaria parasite (preclinical evidence suggests MMV048 is active in both species). The first patients for the phase IIa trial were recruited in 2017, and the initial results look extremely positive. However, before proceeding further, a decision was made to initiate additional non-clinical safety studies to determine precisely which doses can be safely administered to patients. Potential combination drug partners for MMV048 are also being identified using a SCID mouse model of malaria (see pp. 38–39).

In 2017, MMV, in collaboration with the University of Vienna, opened two new clinical research sites near Gondar and Jimma, in Ethiopia. As well as providing sites for conducting the phase IIa study of MMV048, this capacity-building activity has provided a valuable resource that can now be used to conduct other clinical trials, to international regulatory standards.

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**Cipargamin (formerly KAE609)**

Cipargamin is the result of a Wellcome Trust, MMV and Singapore Economic Development Board-supported joint research programme with the Novartis Institute for Tropical Diseases (Singapore), the Genomics Institute of the Novartis Research Foundation (USA) and the Swiss Tropical and Public Health Institute (Switzerland). It is an antimalarial drug with a novel mechanism of action, the first validated new molecular target in 20 years. Furthermore, cipargamin has the potential to block malaria transmission, and to be used for severe malaria due to its ability to kill parasites rapidly.

Ongoing development of the molecule, supported by a Wellcome Trust Grant, includes a phase IIa dose-ranging safety study that was initiated by Novartis in 2017, with the first patient treated in February 2018. Patients will be treated with increasing doses of cipargamin and monitored closely. Doses will be increased in small increments until the optimal dose, offering therapeutic efficacy with an acceptable safety profile, is determined.

In parallel, toxicology and preclinical pharmacology safety assessments of an intravenous formulation of cipargamin for severe malaria are being conducted, with completion expected by the end of 2018. These results, along with patient-safety data from the phase IIa trial, will inform decisions regarding the development of cipargamin for severe or uncomplicated malaria.
Prioritizing molecules for pregnant women

Malaria infection during pregnancy is a significant public health problem with substantial risks for the pregnant woman, her foetus and the new-born child (see p. 22 for more details). MMV is seeking to prioritize the development of drugs safe for use in pregnant women.

Traditionally, most drugs are tested for safety in pregnancy quite late in development (if at all), since in many therapeutic areas a product that cannot be used in pregnancy can still have enormous therapeutic value. However, in the case of malaria, the needs of pregnant women are clear and compelling. Therefore, MMV’s strategy is to identify, as early as possible in development, molecules that might have an acceptable safety profile in pregnancy. This means doing the standard embryo-foetal development studies in parallel with other non-clinical safety assessment or phase I studies. A favourable safety report early on means that these molecules can be prioritized for development.

In addition, with MMV’s support and to help guide the prioritization of drugs for development, a recent review was carried out and published detailing the non-clinical safety of all non-artemisinin antimalarial drugs. The article summarized data that was previously not easily accessible to health experts and will help guide the development of next-generation antimalarial medicines that could have an appropriate safety profile in pregnant women.

**BMC Medicine**

Phase II data on artefenomel/POP combination treatment — the first report of a potential single-dose combination treatment;

MacIntyre H et al. “A randomised, double-blind clinical phase II trial of the efficacy, safety, tolerability and pharmacokinetics of a single dose combination treatment with artefenomel and piperperoxide in adults and children with uncomplicated Plasmodium falciparum malaria.”

**The Lancet Infectious Diseases**

First disclosure of a new antimalarial clinical candidate, AN13762.


**Nature Reviews Drug Discovery**

Article elucidating MMV’s policy on intellectual property, describing it as a key tool to enable timely progression of drug development projects involving multiple partners, while ensuring equitable access to successful products.

Fontaine-Dubois S et al. “Managing intellectual property to develop medicines for the world’s poorest.”

**Malaria Journal**

An update of developments in antimalarial target candidate profiles and target product profiles, illustrating MMV’s key research and development strategies.


**The Lancet Infectious Diseases**

First disclosure of phase I data for DSM265, a compound from a new antimalarial class, also describing the first integrated phase I/human volunteer infection study protocol.

McCarthy JS et al. “Safety, tolerability, pharmacokinetics, and activity of the novel long-acting antimalarial DSM265: a two-part first-in-human phase 1a/1b randomised study.”

**Nature Reviews Disease Primers**

A complete overview of malaria, highlighting the role of vector-control approaches and chemoprevention in reducing the disease burden.

Phillips MA et al. “Malaria.”

**Nature Medicine**

Review of current understanding of how antimalarials act and how drug resistance develops, discussing new strategies to combat resistance and optimize treatment to support malaria eradication efforts.

Blasco B et al. “Antimalarial drug resistance: linking Plasmodium falciparum parasite biology to the clinic.”

**The Lancet**

The Lancet Infectious Diseases

MMV’s first human volunteer infection study for chemoprotection.

Sulyok M et al. “DSM265 for Plasmodium falciparum chemoprophylaxis: a randomised, double blinded, phase I trial with controlled human malaria infection.”

Developing next-generation antimalarials

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Preventing malaria relapse with a single-dose treatment

**ISSUE**
Currently, primaquine is the only treatment available to prevent the relapse of *Plasmodium vivax* malaria. However, as per the primaquine label and WHO recommendations, it is administered once daily for 14 days—a regimen that is hard for patients to comply with, meaning that many are not cured. A single-dose treatment with the potential to improve patient compliance would positively impact *P. vivax* control and elimination efforts.

**ACTION**
MMV and GlaxoSmithKline (GSK) have partnered to develop tafenoquine—a potential new single-dose cure to prevent the relapse of *P. vivax* malaria. In late 2017, registration dossiers were submitted to two stringent regulatory authorities (SRAs), representing a key milestone in the development programme of this important new treatment.

Historically, global malaria efforts have focused on *Plasmodium falciparum* malaria, due to its higher prevalence. This has led to a decrease in the incidence of *P. falciparum* malaria. In comparison, *P. vivax* malaria has not always received adequate attention, despite having the widest geographical distribution of the five species of malaria parasite that infect humans. Moreover, *P. vivax* accounts for about half of malaria cases outside sub-Saharan Africa, often in countries that are close to eliminating malaria.1

Around 8.5 million clinical infections every year are caused by *P. vivax*.2 Many of these are relapses from existing infections that occur in the absence of new infective mosquito bites. This occurs because *P. vivax* parasites can lie dormant in the liver as hypnozoites, reactivating weeks, months or even years after initial infection.

If approved, tafenoquine would be the first new drug in more than 60 years to be registered to prevent the relapse of *P. vivax* malaria and could support some endemic countries in their journey towards malaria elimination.

If approved, tafenoquine would be the first ever single-dose treatment to target the dormant relapsing form of *P. vivax* malaria.

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Anna and Robert discuss the potential impact of tafenoquine in the management of *P. vivax* malaria, and explain the next steps for achieving regulatory approval and country registration.

**What is special about tafenoquine?**

**AT** If approved, tafenoquine would be the first-ever single-dose treatment to target the dormant relapsing form of *P. vivax* malaria, with the potential to significantly improve patient compliance and effectiveness outcomes compared with primaquine.

**Can you tell us about the regulatory review process for tafenoquine?**

**AT** In 2013, the US Food and Drug Administration (FDA) granted tafenoquine a ‘breakthrough therapy’ designation whereby a drug is subject to regulatory measures designed to accelerate the development and review of drugs for serious or life-threatening diseases.

MMV and GSK’s regulatory strategy for tafenoquine was discussed and agreed upfront with two SRAs – the US FDA and the Australian Therapeutic Goods Administration (TGA). Phase III studies have been successfully completed in adults and adolescents over 16 years of age (the target age group for initial registration) supporting submission to these SRAs in 2017. In parallel, a paediatric study is underway to collect data to support subsequent approval of tafenoquine in children.

**What specific challenges have you overcome with tafenoquine?**

**RS** In each endemic country, regulatory requirements and approval timelines vary considerably. To expedite completion of the tafenoquine phase III clinical development programme, we worked closely with the study investigators, as well as with local regulatory and clinical personnel, on the planning and implementation of each study. However, in some regions, such as Asia, we encountered challenges with patient recruitment. To address this, we reached agreements with the FDA and TGA regarding the required number of patients in phase III studies both in total and in each region, so as not to delay the overall marketing application timeline.

**What are the next steps for tafenoquine?**

**AT** Once SRA registration is obtained, MAAs will be filed with the regulatory authorities of *P. vivax*-endemic countries. The associated regulatory dossiers are currently being prepared.

Of note, as with primaquine, tafenoquine could induce haemolysis in patients who have a deficiency in glucose-6-phosphate dehydrogenase (G6PD) enzyme activity, meaning that patients need to be tested for G6PD activity before being given tafenoquine. To facilitate the safe deployment of the treatment, work is therefore ongoing to develop a point-of-care diagnostic test for G6PD deficiency.

Finally, a phase IIIb study has started in Indonesia to assess the co-administration of an artemisinin-based combination therapy (ACT) for blood-stage treatment of *P. vivax* infection with tafenoquine. It is hoped that the results from this study will lend support to achieving registration in some of the countries that currently recommend use of an ACT instead of chloroquine for the management of *P. vivax* blood-stage infection.

**Can you tell us about the working relationship between MMV and GSK?**

**RS** MMV is a great partner and we have good synergy in our working relationship. The tafenoquine joint project team, which includes representatives from the two organizations, meets regularly both virtually and in person. It is this joint team that is working closely together on the FDA and TGA review processes and development of regulatory responses. In addition, MMV provides valuable advice on how to facilitate access to the newly registered medicine in malaria-endemic countries to ensure the best possible patient outcomes – an area in which they have extensive expertise.

Anna Thomas
Senior Director, Regulatory Lead, MMV

Robert Stocken
Director and Global Regulatory Lead, GSK

Anna and Robert discuss the potential impact of tafenoquine in the management of *P. vivax* malaria, and explain the next steps for achieving regulatory approval and country registration.

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