Advancing malaria interventions while supporting the COVID-19 response

Solutions to address the emergence of artemisinin partial resistance in Africa

Artemisinin-based drug combinations were a significant addition to the antimalarial toolbox when introduced in 1971 as a first-line treatment for malaria. Alongside other malaria control tools they have contributed to driving down the disease burden, by 27% between 2000 and 2020.2 Despite the recent emergence of the parasite’s partial resistance to artemisinin, there is no call for panic. Instead, we need to implement three strategies. First, ensure only quality assured, recommended treatments are used. Second, implement strategies such as the use of multiple first-line therapies and low-dose primaquine to help mitigate the threat of resistance. Third, monitor for resistance and change treatments when resistance arises. Finally, ensure that there is a robust pipeline of next-generation drugs to replace today’s medicines when they eventually succumb to resistance.

Currently, a few combinations, such as artemether-lumefantrine are recommended by the World Health Organization (WHO) to treat malaria in areas where artemisinin partial resistance has been observed. MMV is working with partners on several fronts to advance innovation in antimalarial drug discovery and development, to provide more options that can overcome emerging resistance.

MMV’s focus is to combine drugs with powerful antimalarial activity and no cross resistance,3 which are predicted to be able to deliver a cure in patients, have acceptable tolerability and safety, and which manage the risk of resistance emerging. As per our published target product profile, new treatments for uncomplicated malaria would ideally shorten treatment to a single day or would require no more than a 3-day regimen.

Positive clinical results from a novel combination therapy

MMV and Novartis are advancing ganaplacide (KAF156)-lumefantrine in response to the emerging threat of artemisinin partial resistance. The Phase IIb study of the combination yielded positive results. The study tested ganaplacide in combination with a new formulation of lumefantrine optimized for once-daily dosing in adults and children as young as 5 years old with uncomplicated malaria. In cellular assays, this combination appears to stop the formation of gametocytes, indicating it may have clinical potential for blocking transmission of the malaria parasite from humans to mosquitoes.

Unlike most drugs currently in use against malaria, ganaplacide is not an artemisinin derivative but rather an imidazolopiperazine4 that acts on an alternative molecular target yet to be identified, though with a novel Plasmodium falciparum cyclic amine resistance locus marker,6 and it is fully active on strains of malaria in drug-resistant patients. Indeed, ganaplacide is effective even against parasite strains carrying the Kelch 136 mutation that is strongly associated with artemisinin partial resistance.

Another Phase IIb study is currently underway to refine the dosing regimen and explore the dosing in very young children. These findings will be used in a Phase III study to confirm the tolerability, efficacy and safety profile of the selected dose for ganaplacide-lumefantrine; it is planned to begin in 2023, with submission to a stringent regulatory authority in the coming years.
What did the results reveal from the Phase IIb study of the novel ganaplacide-lumefantrine combination in young children with malaria?

Anne Claire Marrast – The Phase IIb study, completed in 2021, tested several dosing regimens of the combination of ganaplacide and a solid dispersible formulation of lumefantrine (also known as LUM-SDF) in adults and children. It allowed us to identify an efficacious dosing regimen with a good safety and tolerability profile, particularly in young children.

Cornelis Winnips – The study results showed that the efficacy of the ganaplacide and LUM-SDF combination against acute malaria in young children was comparable to what we would typically expect from a standard antimalarial treatment.

What is exciting about this combination?

CW – First, ganaplacide has the potential for excellent transmission-blocking activity, based on the in vitro results. Second, if it goes forward into Phase III, it will be the first non-artemisinin-based combination therapy (ACT) to be run in Phase III for treatment of *P. falciparum* malaria for over 20 years.

ACM – Both partner drugs have important characteristics. On the one hand, ganaplacide, which belongs to a new generation of compounds, chemically synthesized, with both pre-erythrocytic and blood-stage activity, allows for rapid clearance of parasites including those carrying the Kelch 13 mutation (a marker of artemisinin partial resistance). On the other hand, as an improved formulation of lumefantrine, LUM-SDF allows for administration once a day rather than twice a day.

What additional challenges were posed by COVID-19?

CW – Due to COVID-related travel restrictions, we experienced operational challenges in terms of monitoring the studies, which had an impact on site engagement. On the operations side, we faced difficulties in getting materials in and out of countries for various reasons, such as shipping restrictions, priorities being focused on COVID-19 rather than on malaria, and reduced flights into each country. This caused delays, but progress was steady.

ACM – The COVID-19 pandemic delayed the start of the second part of the study which was aimed at evaluating efficacy, safety and tolerability in children aged 2 to 12 with several pre-selected dosing regimens based on the results of part 1 of the study.

What are the next steps?

CW – The next step is to select dosage for the final product. We will also decide on a recommendation regarding consumption of food with the drug. We will then test the final dose again in a Phase IIb study and gather efficacy, safety and tolerability data in children all the way down to 6 months of age. While we initiate the Phase III trial programme, we will prepare for the commercial-scale manufacturing of the product in its final dose configuration and formulation suitable for both adults and children. This will happen in parallel over the next 3 years.

ACM – As Cornelis says, once the best dosing regimen is selected, the efficacy, safety and tolerability profile will be confirmed with a large Phase III programme including adults, adolescents and children of all endemic regions, with a particular focus on Africa.

What has it been like to work in partnership on this project?

ACM – Working with Novartis is great because of their professionalism. They see this as a true partnership and the collaboration allows us to bring together Novartis state-of-the-art drug development knowledge and MMV’s expertise in the field of malaria.

CW – Very positive. Novartis has had a collaboration with MMV for many years and on this project since 2016. We really benefit from the unique know-how and expertise of MMV in the field of malaria. It has helped us set up the study in a successful and scientifically sound way, fully meeting the needs of malaria physicians and patients.
### Target product profiles (TPPs)

- **3-day cure, artemisinin-based combination therapies (TPP1)**
- **Uncomplicated malaria treatments and resistance management (TPP1)**
- **Intermittent preventive treatment (TPP1)**
- **Severe malaria treatment/pre-referral intervention (TPP1)**
- **Products targeting prevention of relapse for *P. vivax* (TPP1)**
- **Prophylaxis (TPP2)**

#### Brand names:

#### Target candidate profiles (TCPs)

- **Asexual blood stages** (TCP 1)
- **Relapse prevention** (TCP 3)
- **Causal prophylaxis** (TCP 4)
- **Transmission reduction** (TCP 5, 6)

- **Included in MMV portfolio after product approval and/or development.**
- **DNDi and partners completed development and registration of ASMQ and ASAQ.**
- **Global Fund Expert Review Panel reviewed product – permitted for time-limited procurement, while regulatory/WHO prequalification review is ongoing.**
- **Paediatric formulation**
- **WHO prequalified OR approved/positive opinion by regulatory bodies who are ICH* members/observers.**
- **Via a bioequivalence study.**
- **Past partners are in brackets.**

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* International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
 Coming through: promising combinations and candidates

Combination therapy comprising two or more drugs that preferably have different mechanisms of resistance and act on distinct targets, is the strategy recommended by the WHO to increase drug efficacy and mitigate the risks of drug resistance. In 2021, MMV embarked on the next step of the development process with our partners on several projects.

ZY19489 (Zydus Lifesciences Ltd) + ferroquine

ZY19489 is a novel compound currently being developed in collaboration with Zydus Lifesciences Ltd. The series from which it came was originally identified in a high-throughput screen against asexual blood-stage *P. falciparum* as part of a collaboration between MMV and AstraZeneca at their research facility in India. Phase I studies in healthy volunteers have shown that ZY19489 is well tolerated and demonstrates potent antimalarial activity. Ferroquine was discovered by researchers at the University of Lille, France and advanced into clinical development by Sanofi before it assigned rights for further development to MMV. Modelling and simulation data estimate that both a single dose regimen and a 3-day regimen of 300 mg ZY19489 and 400 mg ferroquine have a good chance of success; both will be tested as part of a European and Developing Countries Clinical Trials Partnership (EDCTP)-funded consortium (SINDOFO) led by Eberhard Karls Universität Tübingen (EKUT).

M5717 (Merck) + pyronaridine

Another promising combination therapy against malaria, currently being developed by Merck, is M5717-pyronaridine. M5717 was identified as part of a collaboration between MMV and the University of Dundee, UK. MMV subsequently assigned the rights for further development of M5717 in malaria to Merck. M5717 is a drug that acts across multiple stages of the malaria parasite life cycle. Phase I studies in healthy volunteers demonstrated that it is well tolerated. However, data from the volunteer infection study identified some potential reduced sensitivity caused by parasites carrying mutations associated with drug resistance. The combination of M5717 with pyronaridine (an antimalarial supplied by Shinpoong Pharmaceuticals) may ensure the efficacy of the combination, as the latter has been in use for decades and still shows antimalarial activity, even against strains that are resistant to other drugs. This combination is exciting, given its potential for use in pregnant women. Phase II studies will start in early 2023 supported by a grant to MMV and partners from EDCTP, called PAMAfrica.
Assessing the use of Pyramax® (pyronaridine-артесунате) in real-world settings

Receiving international regulatory approval of a new medicine is a major milestone, yet it is not the end of the story. MMV works closely with the WHO and National Malaria Control Programmes to ensure that peer-reviewed evidence on its antimalarial medicines supports policy and guideline changes, and thus facilitates supply and patient access in country. This can include post-launch studies to generate safety data about the use of new drugs in real-world settings.

In the case of Pyramax, a 2-year post-launch study conducted in partnership with the Central Africa Network on Tuberculosis, HIV/AIDS and Malaria (CANTAM) and other partners assessed the drug’s utility in real-world settings.

The CANTAM study of over 8,500 malaria episodes across five African countries reported high effectiveness (a Day 28 PCR-adjusted cure rate of 98.6%) and safety and tolerability under conditions similar to everyday clinical practice in community settings.

The study also proved that Pyramax works equally well in both male and female patients, with no difference in the rate of adverse events.

These findings were published in PLoS Medicine (June 2021) and shared with the European Medicines Agency (EMA) and WHO’s Global Malaria Programme.

Based on these data, in July 2021, the updated WHO Guidelines for Malaria confirmed that the previous safety restrictions on pyronaridine-артесунате to treat malaria (see interview with Dr Ntoumi p. 23) were ‘no longer justified’.

MMV continues to assess the use of Pyramax in real-world settings. In particular, an ACT pregnancy registry was established in 2021 in Kenya to gather safety and exposure data on antimalarial use during pregnancy, in particular for newer ACTs such as Eurartesim® (DHA-piperaquine) and Pyramax. The registry has been expanded to Burkina Faso in 2022. Ultimately, it is hoped that the data generated will help reduce gender disparity in the availability of antimalarial interventions.

Pyramax - fast facts

> In 2012, Pyramax® (pyronaridine-артесунате), developed with Shin Poong, was granted a positive scientific opinion from the European Medicines Agency under Article 58 for the treatment of both P. falciparum and P. vivax uncomplicated malaria.

> A total of 2.2 million treatments of Pyramax have since been distributed, a third of which were in granule formulation for children.

> Both Pyramax tablet and granule formulations are cross-referenced on the WHO List of Prequalified Medicines and included in the WHO Model Lists of Essential Medicines for Adults and for Children.

> The adult tablets are approved in 29 countries and the paediatric granules in 19 countries, with further registrations ongoing.
**Why was it important to study Pyramax as part of the CANTAM real-life study?**

In previous randomized controlled clinical trials, pyronaridine-artesunate showed high efficacy and an acceptable safety profile for the treatment of acute uncomplicated *P. falciparum* malaria. However, in some patients, we observed mild to moderate increases in liver enzymes. The CANTAM study was therefore carried out to assess the hepatic safety, tolerability and effectiveness of pyronaridine-artesunate in adults and children in real-life conditions in Africa, including in patients with elevated baseline liver enzymes.

**Why is Pyramax an important addition to the malaria toolbox?**

Pyramax is the only ACT with stringent regulatory approval for the treatment of both *P. falciparum* and *P. vivax* malaria. In addition, the CANTAM study showed it to be well tolerated and efficacious in African patients under conditions similar to real-life clinical practice in Africa. This makes it an important addition to the malaria toolbox.

**Why do we need multiple ACTs and what does this mean in the context of emerging partial drug resistance to artemisinin derivatives in Africa?**

One major challenge being faced in malaria case management is the spread of drug resistance in *Plasmodium* parasites. Partial resistance to artemisinin has been recently reported in Africa and is causing some concern. Resistance is caused by several factors, including overuse of drugs for prophylaxis, incomplete therapeutic treatment of patients and the parasite’s adaptability to drugs. Use of multiple ACTs will not only help reduce the number of clinical cases and treatment failures but may also significantly delay the occurrence of resistance.

**How important were the Community Health Workers (CHWs) in the success of this study?**

The role of CHWs in the CANTAM study was vital and their commitment praiseworthy. They visited the patients on Day 7 and Day 28, following recruitment on Day Zero, and were the principal link between the recruitment facility and patient follow-up at home. They closely followed up and monitored patients in the community, ensured compliance with the treatment guidelines and reported adverse events that might or might not have been related to the pyronaridine-artesunate treatment.

**Has participation in this major real-life study changed the management of malaria in Congo?**

The CANTAM study significantly changed the management of malaria – last year, pyronaridine-artesunate was included in the Congolese national treatment guidelines (NTGs), meaning it is now listed in the NTGs of four out of five participating countries (together with Democratic Republic of Congo, Cameroon and Côte d’Ivoire).

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

As a partner, MMV was accountable to stakeholders and diligently oversaw the continuous monitoring of activities. This allowed quick adjustments to the project when required. The experience has empowered the team with different skill sets for future networking and possible clinical trials.

"Use of multiple ACTs will not only help reduce the number of clinical cases and treatment failures but may also significantly delay the occurrence of resistance."
Deepening our role in supply chain security

Since the global malaria eradication agenda was introduced in 2007, MMV’s operations have been advancing malaria interventions, with significant progress made. Despite the COVID-19 pandemic, MMV and partners continued to advance molecules through the antimalarial drug pipeline and increase access to approved therapies.

We recognize that discovering and developing new, life-saving antimalarial drugs is not enough to guarantee an impact on global health – a secure supply chain is vital if these medicines are to reach the right patients at the right time. COVID-19 highlighted this need, particularly for Africa, and MMV was quick to respond.

Hydroxychloroquine/chloroquine stockpile donations in 2021

The pandemic seriously challenged access to life-saving prevention and treatment for malaria and other major poverty-related diseases in low-income countries. Early in 2020, studies suggested that hydroxychloroquine/chloroquine (CQ) might be used to treat COVID-19 infections, although this was later disproved. This led to a spike in demand for these drugs, and irrational hoarding, placing pressure on existing supply lines and raising concerns that malaria patients in need of CQ may experience supply shortages. With support from The Bill & Melinda Gates Foundation, MMV secured the supply of 120 million tablets to help safeguard access to chloroquine in malaria-endemic countries, where it is used to treat P. vivax blood-stage infections. Significant amounts from this stockpile have already been shipped to countries in support of their P. vivax management efforts.

Monitoring global supply chain security

MMV continued to anticipate and react to potential disruptions to malaria commodity flow due to the COVID-related impact on drug manufacturing and shipment/delivery systems. We doubled down on coordination and support for seasonal malaria chemoprevention campaigns allowing them to continue uninterrupted during the COVID-19 pandemic (p. 16).

Bolstering support for African manufacturing of malaria medicines

This work was instigated partially in response to the disruption caused by COVID-19 and to growing demand for manufacturing solutions closer to where malaria patients live. With funding from Unitaid, we expanded our role in the crucial area of supply chain security. MMV developed, and is implementing, strategies to diversify the supply base of quality-assured therapies and reduce the disproportionate reliance of African countries on drug imports, recognizing that of the continent’s ~375 drug makers only a handful have achieved international quality standards that allow them to compete in tenders for Global Fund procurement. We helped companies achieve WHO-prequalification for antimalarials and supported African manufacturing, for example:

- To address possible manufacturing disruptions due to reliance on a single drug supplier for seasonal malaria chemoprevention (SMC), MMV has been working, since 2015, with S Kant Healthcare Ltd. (India) to develop a 2nd source of child-friendly, affordable, quality-assured formulation of sulfadoxine-pyrimethamine + amodiaquine (SPAQ), called Supyra®, for SMC. In April 2021, Supyra was granted WHO prequalification.
- In 2019, MMV entered into a collaboration with Universal Corporation Ltd., in Kenya to develop sulfadoxine-pyrimethamine (SP) for WHO-recommended chemoprevention for intermittent preventive treatment in pregnancy (IPTp). The product could potentially achieve WHO prequalification in 2022.
- In 2019 and 2020 MMV secured two collaboration agreements with Nigerian companies – Biogaran/ Swipha Ltd. and Emzor Ltd. respectively – to support the development of two further SP products for IPTp, thereby addressing a critical gap in the supply of these quality medicines in high burden countries. Both companies are expected to achieve WHO prequalification in 2022–2023.

By supporting African countries as they diversify their sources of drug supply, MMV is aligned with growing international recognition that regional supply chain security and national healthcare autonomy can be effectively linked.
Continuing R&D support for the COVID-19 response

The COVID-19 pandemic exposed the weaknesses of supply chain systems worldwide, including those of malaria commodities. While remaining true to our mission to discover, develop and deliver effective and affordable antimalarial drugs, in 2021, MMV was quick to respond to malaria supply chain security needs and keep vital therapies accessible to those at risk of the disease. In addition, it continued to contribute its core R&D strengths to the ongoing global effort against COVID-19 in the following areas:

**Compound screening**
- Supported screening of compounds against SARS-CoV-2
- Facilitated screening collaborations between partners from Brazil, Scotland and South Africa among others

**Modelling and simulation**
- Provided ongoing support to several other COVID-19 related research initiatives, including modelling and simulation platforms to predict:
  - potential drug-drug interactions between Ivermectin and ASAQ (in the DNDi-led ANTICOV study10)
  - drug concentrations in human lung epithelium for two antimalarials, amodiaquine and its active metabolite desethylamodiaquine, and pyronaridine

**Clinical development**
- Supported the progression into clinical development of ASAQ (in ANTICOV11 and the MMV-sponsored ReACT studies); and Pyramax® (pyronaridine-artesunate) (in the ReACT study).
- Assembled an expert virology advisory board and provided technical advice to Shin Poong, that had completed Phase Ib trials of Pyramax to treat mild-to-moderate COVID-19 patients in Korea.

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10 ANTICOV: https://dndi.org/research-development/portfolio/anticov
11 The ANTICOV clinical trial responds to the urgent need to identify treatments that can be used to treat mild and moderate cases of COVID-19 early and prevent spikes in hospitalizations that could overwhelm fragile and already overburdened health systems in low-resource settings.