Developing the next generation of medicines

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↖ Schoolchildren, Mangalore, India

Meeting the challenge of antimalarial drug resistance

Progress against malaria has plateaued in recent years, and the global disease burden remains high, with some 247 million cases and 619,000 deaths annually.[1] To get back on track, multiple tools and approaches will be needed, including new antimalarial medicines to help manage the emergence and spread of resistant parasites.

Evolution of microbes to resist the medicines used to fight them threatens the public health response to many infectious diseases, including malaria. To delay the emergence of resistance, malaria treatment combines drugs with different mechanisms of action, so parasites resistant to one component remain vulnerable to another. Decreased sensitivity to artemisinin derivatives, the mainstays of treatment, has been observed for two decades in South-East Asia, and more recently in Africa.[2,3,4] However, resistance has not yet developed to all partner drugs, leaving several key compounds including lumefantrine and pyronaridine largely unaffected. The emergence of parasites completely resistant to artemisinins or to all their partner drugs would mean loss of the first line of defence in Africa – artemisinin-based combination therapies (ACTs[5]). This would pose a major threat to control and elimination efforts.

In November 2022, the World Health Organization (WHO) released its 'Strategy to respond to antimalarial drug resistance in Africa'.[6] This Strategy is based on four pillars, each comprising a set of interventions to be adapted to specific contexts and implemented at local, regional and global levels: 1) strengthening surveillance of antimalarial resistance; 2) optimizing and better regulating the use of medicines and diagnostics to reduce selection for resistance; 3) limiting the spread of drug-resistant parasites; and 4) stimulating research and innovation to develop new tools against resistance and to better leverage existing ones.

Before discussing the role of new medicines, the WHO Strategy highlights the need to optimize the use of existing ones. MMV exemplifies this approach in several ways. Firstly, by advocating use of multiple first-line treatments (MFTs) within a population: we have been leading pilot implementation studies in Burkina Faso and Kenya that aim to prolong the useful lives of medicines by delaying development of resistance to individual components.[7] Secondly, we are partnering with Fosun Pharma, Marubeni Corporation and the Mahidol Oxford Tropical Medicine Research Unit (MORU) to develop triple-drug artemisinin combination therapies as fixed-dose combinations – effectively MFTs in a single pill.

> "The earlier we have new medicines ready to be deployed and the faster the world is prepared to introduce them, the better chance we stand of beating resistance."
>
> — **Dr Sujata Vaidyanathan**, Head Global Health Development Unit, Novartis

1. World Malaria Report 2022: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2022
2. Uwimana A *et al.* "Emergence and clonal expansion of *in vitro* artemisinin-resistant *Plasmodium falciparum* kelch13 R561H mutant parasites in Rwanda" *Nat Med.* 26(10):1602–8 (2020), doi: 10.1038/s41591-020-1005-2
3. Balikagala B *et al.* "Evidence of Artemisinin-Resistant Malaria in Africa" *N Engl J Med.* 385(13):1163-71 (2021), doi: 10.1056/NEJMoa2101746
4. Artemisinin resistance is linked to specific mutations in the parasites, notably affecting the gene kelch13; the presence of these mutations is being closely monitored by WHO. For further information about geographical distribution of artemisinin resistance, see https://apps.who.int/malaria/maps/threats/
5. Consisting of an artemisinin derivative and a partner drug. Combinations of three different drugs are also being investigated.
6. World Health Organization. Strategy to respond to antimalarial drug resistance in Africa (2022). https://www.who.int/publications/i/item/9789240060265
7. Boni MF *et al.* "Benefits of using multiple first-line therapies against malaria" *Proc Natl Acad Sci USA.* 105(37):14216–21 (2008), doi: 10.1073/pnas.0804628105

Finally, we are working to prevent the spread of resistant parasites by making the WHO-recommended transmission-blocking medicine primaquine available at doses small enough for use in children.

Our response to antimalarial resistance also includes monitoring for resistance and changing treatments when it arises; delivering only high-quality, WHO-prequalified medicines to ensure efficacy; advocating against use of substandard or counterfeit drugs;[8] developing discovery networks and assay platforms to identify the most promising compounds for fighting malaria and other pathogens;[9] giving researchers open access to compounds and knowledge to facilitate drug discovery;[10] and supporting National Malaria Control Programmes (NMCPs) and other partners in delivering medicines to the people who need them most.[11]

The best defence against antimalarial resistance is a robust pipeline of medicines to replace those losing their efficacy. To date, MMV's partnerships with pharmaceutical and biotech companies, research institutions, governmental, international and non-governmental/non-profit organizations, donors and clinical centres in malaria-endemic countries have resulted in 15 medicines now in clinical use, with 13 further compounds in clinical development.[12]

MMV prioritizes molecules that are highly active against existing resistant strains, with low potential to generate future resistance – particularly compounds for which no resistant strains can be developed in the laboratory or isolated clinically. We aim to develop potent combination medicines that are unlikely to produce resistance to other drugs, have good safety profiles, and can both cure infection and manage the risk of resistance, as well as compounds that can block transmission and/or protect against infection.

Because incomplete cure also contributes to the development of resistance, we and our partners seek to improve treatment adherence by developing patient-friendly medicines with shorter and simpler treatment regimens, ideally requiring only a single dose.

8. See Chapter 5 and https://fightthefakes.org
9. See Chapter 4.
10. Including compounds active against drug-resistant strains of other pathogens; see Chapter 4.
11. See Chapters 5 and 6.
12. See portfolio on page 15.
13. Ogutu B *et al.* "Safety and efficacy of KAF156 (ganaplacide) in combination with lumefantrine-SDF in children 2–12 years with uncomplicated *Plasmodium falciparum* malaria. Part B of a phase 2 clinical trial." Presented at American Society of Tropical Medicine & Hygiene 2022 Annual Meeting (30 October–3 November 2022; Seattle, Washington, USA). Abstract no. 1472. See also https://clinicaltrials.gov/ct2/show/NCT03167242
14. Ganaplacide is the result of a Wellcome Trust, MMV and Singapore Economic Development Board-supported joint research programme with the Novartis Institute for Tropical Diseases (NITD), the Genomics Institute of the Novartis Research Foundation, and the Swiss Tropical and Public Health Institute (Swiss TPH). Phase II and III studies of this compound are funded by the European and Developing Countries Clinical Trials Partnership (EDCTP), which is supported by the European Union.
15. Yipsirimetee A *et al.* "Assessment *In Vitro* of the Antimalarial and Transmission-Blocking Activities of Cipargamin and Ganaplacide in Artemisinin-Resistant *Plasmodium falciparum*" *Antimicrob Agents Chemother.* 66(3):e0148121 (2022), doi: 10.1128/AAC.01481-21

Ganaplacide/lumefantrine advancing to Phase III

In November 2022, MMV and Novartis announced the decision to advance to Phase III (confirmatory studies in patients) with a novel non-artemisinin combination, ganaplacide/lumefantrine, for treatment of acute, uncomplicated *Plasmodium falciparum* malaria. This decision was based on promising results in a Phase IIb study in adults and older children.[13]

Ganaplacide,[14] a fast-acting compound with a new mechanism of action, has been combined with a new formulation of lumefantrine optimized for once-daily dosing, as opposed to twice daily with artemether-lumefantrine. Ganaplacide is active against both *P. falciparum* and *Plasmodium vivax* parasites, including those resistant to current medicines. The combination not only has potential to cure patients with 3 days of treatment but may also block parasite transmission from humans to mosquitoes.[15]

A large Phase III trial, planned to start in late 2023, will compare the efficacy of ganaplacide/lumefantrine solid dispersible formulation (SDF) to the current gold standard, artemether-lumefantrine (Coartem® *Dispersible*). It will be conducted in collaboration with the West African Network for Clinical Trials of Antimalarial Drugs-2 consortium (WANECAM-2; funded by the European and Developing Countries Clinical Trials Partnership (EDCTP)), and will include partner clinical sites in Burkina Faso, Gabon, Mali and Niger as well as other sites in sub-Saharan Africa and India.

> We are increasingly seeing parasites with decreased sensitivity to artemisinin, even in Africa. This new combination will increase the number of options available to countries facing artemisinin resistance and play a key role in slowing down its spread. It is urgently needed to treat children in malaria-endemic countries.
>
> — **Dr Timothy Wells**, Chief Scientific Officer, MMV

Intravenous cipargamin (KAE609) in severe malaria

Severe malaria is a life-threatening condition resulting from complications of malaria infection. Patients may develop anaemia, hypoglycaemia, respiratory distress, convulsions and coma, which can result in death within hours.[16] Every minute counts when treating severe malaria, particularly in young children. However, in many endemic areas, access to diagnosis and treatment is limited. In remote settings, community healthcare workers can provide initial diagnosis and basic medications, referring patients to more advanced facilities when necessary. WHO currently recommends using injectable artesunate for severe malaria.[17]

Cipargamin (KAE609), discovered by a Novartis-led consortium funded by MMV and other partners,[18] targets *Plasmodium falciparum* Ca^{2+} ATPase (*Pf*ATP4), a parasite cell membrane channel that is the first validated new molecular target for malaria in more than 20 years. In a proof-of-concept study in Thailand, cipargamin rapidly cleared parasites from the blood of adults with uncomplicated *P. falciparum* or *P. vivax* malaria.[19] Subsequent studies have established its effective dose and demonstrated its rapid onset of effect, as well as confirming a good safety profile.[20]

Novartis is investigating a new intravenous cipargamin formulation for treatment of severe malaria, with funding from the Wellcome Trust. A study of this formulation in healthy volunteers (Phase I), completed in 2020, demonstrated good tolerability. A Phase II study of intravenous cipargamin is being conducted in several African countries and India, in collaboration with the PAMAfrica[21] consortium (which is led by MMV and funded by the EDCTP). The study aims to identify a well-tolerated and effective dose for treatment of adults and children with severe malaria.

→ Young patients, Nchelenge, Republic of Zambia

16. Trampuz A *et al.* "Clinical review: Severe malaria" *Crit. Care* 7(4):315-23 (2003), doi: 10.1186/cc2183
17. World Health Organization. WHO Guidelines for Malaria, 25 November 2022. WHO/UCN/GMP/2022.01 Rev.3. https://apps.who.int/iris/handle/10665/364714
18. This consortium is funded by MMV, the Wellcome Trust and the Singapore Economic Development Board in collaboration with the Swiss TPH. Cipargamin is being developed by Novartis in collaboration with MMV and EDCTP, with financial and technical support from the Wellcome Trust.
19. White NJ *et al.* "Spiroindolone KAE609 for *Falciparum* and *Vivax* Malaria" *N Engl J Med.* 371(5):403–10 (2014), doi: 10.1056/NEJMoa1315860
20. Schmitt EK *et al.* "Efficacy of Cipargamin (KAE609) in a Randomized, Phase II Dose-Escalation Study in Adults in Sub-Saharan Africa with Uncomplicated *Plasmodium falciparum* Malaria" *Clin Infect Dis.* 74(10):1831-9 (2022), doi: 10.1093/cid/ciab716
21. A group of nine public and private-sector research and development partners across Africa and Europe, led by MMV and including IRSS (*Institut de Recherche en Sciences de la Santé*, Burkina Faso), IDRC (*Infectious Diseases Research Collaboration*, Uganda), GRAS (*Groupe de Recherche Action en Santé, Burkina Faso*), Fundação Manhiça (Mozambique), ISGlobal (Barcelona Institute for Global Health), CERMEL (*Centre de Recherches Médicales de Lambaréné*, Gabon), Eberhard Jarls Universität Tübingen, Novartis and Merck KGaA and with funding from the EDCTP as well as from the consortium partners. See https://www.pamafrica-consortium.org

Chemoprevention: a continuing need

Preventing infection is always a better option than treating disease. The present mainstays of malaria prevention involve either targeting the vector (mosquito) with bed nets or larvicides or protecting people using medicines (chemoprevention). Chemoprevention has proven to be efficacious and cost-effective, particularly in children where malaria transmission is seasonal. In 2022, almost 50 million children under 5 years old were protected by seasonal malaria chemoprevention (SMC), and almost 20 million pregnant women took some form of malaria prophylaxis.[22]

> "Preventing infection is always a better option than treating disease."

SMC for children requires 3 days of medicine every month. Anything that would be simpler, such as a long-acting injectable (LAI) formulation for chemoprevention or a new oral medicine with once-monthly dosing, would represent a valuable alternative. Long-acting medicines have already proven their practicality and effectiveness with HIV and show considerable promise for use against malaria.

Two newer approaches to long-acting protection involve vaccines or monoclonal antibodies. The current vaccine, RTS,S (Mosquirix™) from GSK, is only partially protective, and is relatively expensive. Recent studies have shown that it is most effective when given in addition to SMC in small children.[23] New vaccines are under development, but because the immunity resulting from natural malaria infection cannot completely prevent future infection, it is unlikely that any new vaccine will produce a paradigm shift in terms of protection. It will therefore remain essential to be able to offer multiple levels of protection: nets, vaccines *and* medicines. The other new area of development over the last year is the potential use of monoclonal antibodies as once-per-season injections to protect children; MMV is partnering with the US National Institutes of Health to explore this possibility.

Long-acting injectables for chemoprevention

Long-acting chemoprevention is an important area of research and development for MMV, and has the potential advantages of high efficacy, simplicity and low cost.

Working originally with Calibr (a non-profit research institute in San Diego), Oregon Health & Science University, and subsequently Janssen Pharmaceuticals, MMV is continuing development of a long-acting injectable combination with potential to protect children – and possibly adults – for several months.

The first component, MMV371, is a prodrug[24] of atovaquone, one of the two active ingredients of the travellers' drug Malarone®. Once released into the circulation, MMV371 is rapidly converted to the active molecule, atovaquone. A slow-release formulation for injection has completed preclinical safety testing, and a first-in-human study is planned to start in 2023. The current prediction is that a single injection corresponding to the proposed human dose could provide protection for more than 3 months.

An important consideration with a long-acting injectable is to prevent the selection of resistant parasites by including a second active molecule. MMV tested all currently registered medicines to find potential partner compounds, but none was suitable. However, a drug discovery candidate known as MMV055 (previously published as ELQ300; discovered in an MMV-supported collaboration with Oregon Health & Science University) has suitable physico-chemical properties and meets all other necessary criteria.

Both compounds work by binding to mitochondrial cytochromes, disrupting energy production and thereby killing both blood-stage and liver-stage parasites. Crucially, they bind to their target at different sites, so parasites that become resistant to either compound will remain sensitive to the other. Moreover, cell biology studies show that there is synergy between the two molecules: the impact of the combination is greater than would be predicted from the two used separately.

If the slow-release MMV371 injection shows acceptable safety and suitable pharmacokinetics[25] in Phase I, then the plan is to complete the preclinical package for MMV055, both alone and in combination with MMV371, to allow clinical assessment as soon as possible.

Pyronaridine/piperaquine combination

The burden of malaria chemoprevention is currently carried by two medicines: sulfadoxine-pyrimethamine (SP), used for chemoprevention during pregnancy, and SP + amodiaquine (SPAQ), used for SMC in children.[26] As these medicines are used to protect tens of millions of women and children in Africa, the threat of resistance is omnipresent and new options for chemoprevention are urgently needed. This is particularly true for protection of women during pregnancy: chemoprevention with SP can be used only after the first trimester, there are no data to support use of vaccines during pregnancy, and current monoclonal antibodies are unlikely to be cost-effective for adults.

MMV's strategy for addressing this challenge includes the re-combination of compounds that are now used individually for malaria treatment. A review of approved products was conducted as part of a WHO/MMV workshop in 2020 to prioritize combinations potentially suitable for malaria chemoprevention in pregnancy, leading to the selection of a pyronaridine/piperaquine combination. Pyronaridine and piperaquine have been in clinical use for more than 20 years for uncomplicated malaria, as part of the ACTs Pyramax® (pyronaridine-artesunate) and Eurartesim® (dihydroartemisinin-piperaquine) respectively, but have not been administered in combination previously. The new combination has potential for requiring only a single dose per month. Current clinical safety data from the two ACTs suggest that a pyronaridine/piperaquine combination may be suitable for use in pregnant women.

The safety and pharmacokinetics of the combination were tested in a study in healthy volunteers of sub-Saharan African origin, which finished in September 2022.[27] A Phase II study to assess the duration of protection in African adults is planned in 2023.

22. See Chapter 5.
23. The combination further reduced the risks of clinical malaria, hospitalization for severe malaria and death from malaria by approximately 60%, 70% and 75% respectively, compared to the vaccine alone; Chandramohan D *et al.* "Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention" *N Engl J Med.* 385(11):1005-17 (2021), doi: 10.1056/NEJMoa2026330
24. A precursor of a drug that is converted to its active form by metabolic processes.
25. Characteristics describing how a drug is absorbed, distributed, metabolized and excreted from the body.
26. See Chapter 5.
27. Conducted in collaboration with Richmond Pharmacology and PharmaKinetic Ltd; a summary can be found at https://clinicaltrials.gov/ct2/show/results/NCT05160363

Promising candidates in early development

Thanks to the success of our discovery collaborations, there are now several highly promising molecules in early clinical development that could form part of a next-generation cure for uncomplicated malaria. The current plan is to combine up to three molecules, with a view to shortening treatment and providing protection against future emergence of resistance.

- **MMV533 (discovered in partnership with Sanofi)** is fast-acting, with a low predicted human dose (around 1 mg/kg)[28] and a long half-life[29] in humans. No resistance against MMV533 has been observed in cell biology studies or in clinical isolates. The first-in-human study and a volunteer infection study[30] were completed in September 2022.

- **GSK701 (GSK)** is fast-acting, with an intermediate predicted human dose (>5 mg/kg) and half-life, and is highly active against resistant strains. Its mechanism of action has been identified as inhibition of the *P. falciparum* enzyme acyl-CoA synthetase 10/11. The first-in-human study has been completed, and the compound will be tested for activity in a volunteer infection study at QIMR Berghofer (Brisbane, Australia) in 2023.

- **INE963 (Novartis)** is fast-acting, with an intermediate predicted human dose (>5 mg/kg) and half-life (around 150 hours). No resistance has been observed in cell biology studies or in clinical isolates. The first-in-human study has completed dosing, and the compound will be tested for activity in a Phase II study in African adults, as monotherapy and in combination with cipargamin, in 2023.

Two further compounds, both of which would form part of a multiple-drug treatment-shortening combination, are currently in preclinical development:

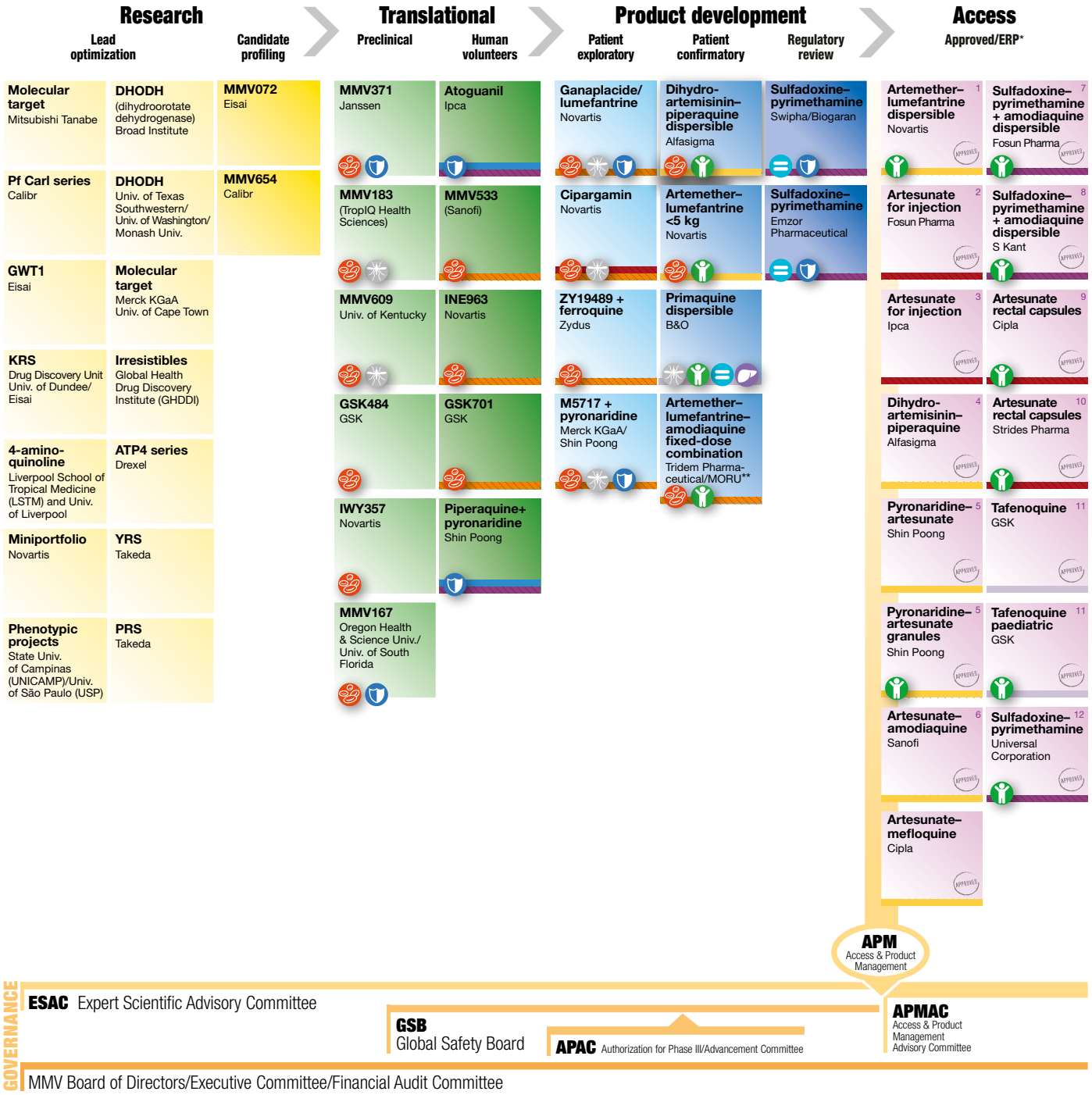
- **GSK484 (GSK; 2021 Project of the Year)** is a fast-acting compound with a low predicted human dose (1 mg/kg) and a long predicted human half-life (around 200 hours). No resistance has been observed in cell biology studies. A first-in-human study is planned in 2023.

- **MMV183 (discovered in partnership with TropIQ Health Sciences)** is a fast-acting compound with a low predicted human dose and short predicted half-life. It has a novel mechanism of action: inhibition of the enzyme acetyl-CoA synthetase. It is presently being scaled up in preparation for a first-in-human study.

→ In a hospital laboratory in Kilifi, Kenya

28. Burrows JN *et al.* "New developments in anti-malarial target candidate and product profiles" *Malar J.* 16(1):26 (2017), doi: 10.1186/s12936-016-1675-x. Erratum in: *Malar J.* 16(1):151 (2017).
29. Meaning that the compound stays in the blood for a long time.
30. Studies in which healthy volunteers are injected with a low number of drug-sensitive parasites before receiving an experimental drug 8 days later to assess its blood-stage activity.

MMV-supported projects



Target product profiles (TPPs)

- 3-day cure, artemisinin-based combination therapies (TPP1)
- Non-artemisinin therapy for 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)
- Chemoprophylaxis (TPP2)

Brand names: 1. Coartem® *Dispersible*; 2. Artesun®; 3. Larinate® 60 mg; 4. Eurartesim®; 5. Pyramax® tablets or granules; 6. ASAQ Winthrop®; 7. SPAQ-CO™; 8. Supyra®; 9. 100 mg Artesunate Rectocaps; 10. Artecap™; 11. *Krintafel/Kozenis* (Trademarks owned or licensed by GSK); 12: Wiwal®

Target candidate profiles (TCPs)

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

- Paediatric formulation
- WHO prequalified OR approved/positive opinion by regulatory bodies who are ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) members/observers
- Via a bioequivalence study
- (-) Past partners are in brackets

* ERP: Global Fund Expert Review Panel
** MORU: Mahidol Oxford Tropical Medicine Research Unit