Malaria

- takes a child’s life every 2 minutes
- kills an estimated 405,000 people each year
- can kill within 24 hrs of symptom onset
- is both a cause and consequence of poverty

Medicines for Malaria Venture (MMV)

is recognized as a leading product development partnership in the field of antimalarial drug research and development. It was established as a foundation in 1999 in Switzerland.

MMV’s mission

is to reduce the burden of malaria in disease-endemic countries by discovering, developing and delivering new, effective and affordable antimalarial drugs.

MMV’s vision

is a world in which these innovative medicines will cure and protect the vulnerable and under-served populations at risk of malaria, and help to ultimately eradicate this terrible disease.
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‘Bending the curve’
to malaria eradication

Message from the Chairman and CEO

2019, our twentieth year, gave MMV and our partners many reasons to celebrate. Established in 1999 to reignite stalled research and development into malaria medicines, MMV has since built the richest malaria drug pipeline in history, with 13 new antimalarials now treating patients. These medicines have contributed to saving more than 2.2 million lives and are helping bend the curve towards the eradication of malaria.

However, around 405,000 people continue to die of malaria every year and in 2019 the World Health Organization (WHO) Strategic Advisory Group on Malaria Eradication (SAGme) concluded that; “using current tools, we will still have 11 million cases of malaria in Africa in 2050.”1 Added to this, at the time of writing in 2020, the situation has been further compounded by the novel coronavirus disease (COVID-19) pandemic. Modelling data points to a potentially catastrophic combined impact of COVID-19 and malaria on many endemic countries.2 In the worst case, this could lead to a tragic doubling in lives lost to malaria in 2020.2

In these challenging times, we are firmly focused on two goals: the WHO Global Technical Strategy for Malaria 2016–2030’s ambitious target to eliminate malaria from at least 35 countries by 2030; and the Lancet Commission on malaria eradication’s ‘bold but attainable goal’ to achieve eradication by 2050 by ‘bending the curve’ to accelerate the decline in malaria cases and deaths. To this end, MMV has several ‘strategic levers’ in its back pocket.

As per the Lancet Commission report, several trajectories are possible in our efforts to defeat malaria, as illustrated in Figure 1 and explained in Table 1 (p. 6). The role of medicines as ‘strategic levers’ will be key to each of these trajectories and frames the way we look at our work.

Figure 1: Bending the curve: four trajectories based on WHO SAGme and the Lancet Commission reports on malaria

See accompanying Table 1 on page 6


“...”

"These medicines have contributed to saving more than 2.2 million lives and are helping bend the curve..."
Enhancing control/elimination

The first step to bending the curve means improving the way malaria patients are treated, that is, better case management. MMV has been working with partners to provide a range of treatment options tailored to addressing unmet medical needs, across different populations. In 2019, we welcomed WHO’s information note on Pyramax® (pyronaridine-artesunate), which stated that “[i]t can be considered a safe and efficacious ACT for the treatment of uncomplicated malaria in adults and children weighing 5 kg and over in all malaria-endemic areas”. By deploying medicines like Pyramax, we can safeguard the efficacy of current first-line artemisinin-based combination therapies (ACTs), for longer (p. 14–15).

Improving case management of relapsing malaria is critical to achieving elimination, specifically of Plasmodium vivax, which accounts for half of all cases outside sub-Saharan Africa. Tafenoquine, the first single-dose radical cure for relapsing P. vivax malaria, was initially approved by the US Food and Drug Administration and the Australian Therapeutic Goods Administration in 2018. In 2019, it was granted authorization in the first malaria-endemic country, Brazil. Preparations are now underway to gather data in Brazil and other countries to guide optimal implementation of tafenoquine, together with a G6PD test to determine which patients can receive the medicine (p. 29–29).

Enhancing malaria control and elimination requires not only essential tools and data, but also investment to boost capability and capacity in endemic countries, by training healthcare workers and developing research capacity. MMV has been working with partners to do just that right across the research and healthcare continuum, from providing drug discovery assets (p. 35) and support to endemic-country scientists to developing training material and easy-to-understand information on product packaging.

Aiming for eradication

One of the key reasons new tools will be needed to eradicate malaria is antimicrobial resistance (p. 11–12). Several ACTs, which are a first-line treatment for acute, uncomplicated malaria in approximately 80 countries, are now failing against Plasmodium falciparum in parts of South East Asia, and markers of partial artemisinin resistance have also been reported in Rwanda. MMV and partners are catalysing the development of next-generation combination therapies to combat resistance with two front runner combinations being tested in Phase II in Africa – artefenomel-ferroquine and ganaplacide-lumefantrine (p. 12–13).

Given the high risk of clinical failure in drug development, it is critical to have other drugs in the pipeline that could be paired up to form combinations. MMV and partners already have a number of novel drug candidates moving forward in development, including ciparigam, M6717 and MMV253, and each year one or two more join this list (p. 18–19). The availability of drugs that are easy to administer, and so facilitate enhanced treatment compliance, can reduce malaria transmission and provide a meaningful duration of post-treatment protection will accelerate the path to eradication. For this reason, compounds are also selected for their ability to block transmission and protect against malaria. In 2019, to accelerate the development and selection of new combination therapies, MMV launched the Malaria Drug Development Catalyst (p. 30), a new legal and scientific platform that helps to identify the best combinations of compounds to take forward and allow for an ease of exchange between partners.

A tale of two curves

The resurgence of malaria was initially depicted in Figure 1 in grey – a nod to our hope that this would be a less probable scenario. The COVID-19 pandemic has changed that, making this scenario, sadly, more probable. In parallel with our work to bend the malaria curve, MMV is now supporting global efforts to flatten the COVID-19 curve of transmission and infection. We are deploying our unique assets and expertise to help lessen the impact of COVID-19, for example, by working with our partners to understand whether any current antimalarials can be repurposed for COVID-19, alongside the WHO and as part of the COVID-19 Clinical Research Coalition.

COVID-19, however, is not the only pandemic that threatens the world. Ebola, Zika, dengue and influenza all endanger our interconnected way of life. We urgently need to discover new drugs to fight these global health emergencies. MMV Open is a pioneering initiative to support R&D efforts in malaria and other tropical diseases by providing access to open-source libraries. In 2019, a molecule arising from work by the London School of Hygiene & Tropical Medicine and Salvensis on MMV’s Malaria Box collection was transferred to Merck for development as a potential treatment for schistosomiasis. In 2020, focus will no doubt fall on MMV and DNDi’s Pandemic Response Box, which contains compounds with not only antimalarial, but also antiviral, antibacterial and antifungal properties.

During the COVID-19 pandemic, a primary focus is safeguarding access to vital medicines to ensure that malaria patients, particularly children under 5 years of age who are at greatest risk of malaria morbidity and mortality, can access life-saving medicines and emergency care. Across the world, the COVID-19 pandemic has surfaced a deep anxiety for the loss of our loved ones; an anxiety that echoes the deep, unheard concern of millions of parents of malaria-infected children every day. The pandemic has also resurfaced the critical role of research and development for new medicines as well as that of ensuring the security of their supply. The need to reduce the burden of malaria in disease-endemic countries has never been more acute. This mission drives our redoubled efforts to bend the curve to malaria eradication as, along with our partners, we continue into the next decade of discovery, development and delivery of new, effective and affordable antimalarial drugs.

“...two front runner combinations (are) being tested in Phase II in Africa.”

3 In individuals who are deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD), 8-aminoquinolines can destroy red blood cells, potentially causing anaemia. To help identify patients eligible for treatment, GSK’s partner PATH has fostered the development of a quantitative point-of-care G6PD diagnostic test, which is now approved in nine P. vivax-endemic countries.
<table>
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<th>How MMV will contribute</th>
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<tr>
<td><strong>1. Status quo (control)</strong></td>
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| **2. Beyond the status quo: enhanced control and elimination** | APM  
(enhanced case management capacity and programme implementation)  
(Increased international and domestic financing)  |
| | Improve real-time access to data to guide programme implementation  
Accelerate introduction of new interventions e.g. to ensure there are multiple first-line therapies available  
Support initiatives to enhance rural access  
Generate evidence to expand use of current interventions (patient populations and use cases)  
R&D  
(Repurpose drugs for preventive treatment  
Integrate existing transmission-blocking drugs into mainstream treatment  
Develop next-generation cures for uncomplicated malaria  
Support capacity and competency development)  
Advocacy (with RBM, MNM & malaria funders)  
(Communicate that malaria is an indicator & enabler of health security, UHC and maternal/child health) |
| **3. The road to eradication** | R&D  
(New tools)  
(Increased financing)  |
| | All new MMV medicines to address resistance  
Transition towards second-generation, single-exposure radical cures  
Develop medicines with enhanced transmission-reduction, including endectocidal activity  
Develop new chemoprotection therapies, including long-acting parenterally-administered drugs and monoclonal antibodies, to prevent reintroduction  
APM  
(Work with partners to enhance data collection to refine TPPs and guide future implementation)  
Advocacy (with RBM, MNM & malaria funders)  
(Communicate the value-case for eradication to maintain political and corporate support)  
| |
| **4. Preventing resurgence** | APM  
(Drug resistance)  
(Control efforts diminish owing to competing priorities, reduced political or corporate will, or reduced funding)  |
| | Identify and help resolve supply issues  
Prolong lifespan of current medicines (MFTs)  
R&D  
(When resistance occurs, be ready to respond with new medicines by accelerating viable 2–3 dose combinations  
Alternative treatment(s) for severe malaria  
Advocacy (with RBM, MNM & malaria funders)  
(Position malaria within the AMR agenda  
Support policymakers to make timely decisions about improved drug management strategies in times of increasing malaria resistance/resurgence  
Support partners to realize external CSR value and maintain internal commitment)  |

AMR, antimicrobial resistance; APM, Access and Product Management; CSR, corporate social responsibility; MFT, multiple first-line therapies; MNM, Malaria No More; R&D, research and development; RBM, Roll Back Malaria Partnership to End Malaria; SAGme: WHO Strategic Advisory Group on Malaria Eradication; TPP, target product profile; UHC, universal health coverage.

See accompanying Figure 1 on page 4
### Target product profiles

- **3-day cure, artemisinin-based combination therapies (TPP1)**
- **Uncomplicated malaria treatments for single-exposure radical cure (SERC) and/or 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)**


### Research 

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<th>Research</th>
<th>Candidate profiling</th>
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<td>Phenotypic lead Mitsubishi Tanabe</td>
<td>Molecular target DHOOH Broad Institute</td>
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### Product development 

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### Access 

- **Approved/ERP**
  - Artesunate-mefloquine Cipla
  - Sulfadoxine-pyrimethamine + amodiaquine dispersible Fosun Pharma
  - Artesunate for injection Ipca
  - Pyronaridine-artesunate granules Shin Poong
  - Artesunate rectal capsules Strides Pharma
  - Pyronaridine-artesunate granules Shin Poong
  - Artesunate-amodiaquine Sanofi

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**ESAC** Expert Scientific Advisory Committee

**GSB** Global Safety Board

**APAC** Authorization for Phase III/Advancement Committee

**APM** Access and Product Management Advisory Committee
**Key achievements 1999–2019**

**Malaria killed over 1 million people, hitting poor people hardest**

**1999**
Against a backdrop of a virtually empty antimalarial drug pipeline, MMV is launched to develop new antimalarials for vulnerable populations.

**2000**
First industrial and academic organizations become part of MMV’s network: GSK, University of Bristol, London School of Hygiene & Tropical Medicine, SmithKline Beecham, University of California, Roche, University of Nebraska and Swiss TPH.

**2001**
MMV announces core management team.

**2002**
MMV signs agreement with Shin Poong Pharma and WHO-TDR to develop Pyramax® (pyronaridine-artesunate).

**2003**
After a successful stakeholder review, MMV becomes a “3D” organization, adding “delivery” to its “discovery and development” activities.

**2004**
MMV signs agreement with Alfasigma S.p.A., Oxford University and Holley-Cotec to develop Eurartesim® (dihydroartemisinin-piperaquine).

**2005**
MMV signs agreement with Altana and Dainippon Sumitomo Pharma (Daiwa) to develop Pyramax®.

**2006**
MMV announces collaboration with GSK for development of tafenoquine for radical cure of P. vivax malaria.

**2007**
Major Phase III studies completed for Eurartesim® and Pyramax® involving more than 6,000 patients.

**2008**
First patient enrolled in Pyramax® trial at the Hospital for Tropical Diseases, Mahidol University, Bangkok.

**2009**
MMV, Drugs for Neglected Diseases initiative (DNDi) and Sanofi launch largest post-approval antimalarial safety cohort event monitoring study of artemisinine-amodiaquine (ASAQ Winthrop®) involving 15,000+ patients in Ivory Coast.

**2010**
Malaria Box launched to catalyse malaria and neglected diseases drug research.

**2011**
3rd medicine: Alfasigma S.p.A.’s Eurartesim® for acute uncomplicated P. falciparum malaria receives EMA regulatory approval.

**2012**
Over 5 million chemical compounds screened directly against the malaria parasite by MMV and partners, yielding 25,000+ new chemical starting points.

**2013**
MMV, Novartis and partners discover novel antimalarial drug candidate, KAE609 (cipargamin).

**2014**
New Model comes on stream at QIMR Berghofer in Australia to accelerate drug development, allowing drug candidates to be tested in healthy individuals infected with malaria in carefully controlled conditions.

**2015**
Bill & Melinda Gates Foundation calls for new global commitment to malaria eradication.

**2016**
The ‘ Consortium for ACT Private Sector Subsidy (CAPSS) launches pilot in Uganda to demonstrate impact on access from subsidizing ACT pricing in rural private sector.

**2017**
MMV announces collaboration with GSK for development of tafenoquine for radical cure of P. vivax malaria.

**2018**
The ‘ Consortium for ACT Private Sector Subsidy (CAPSS) launches pilot in Uganda to demonstrate impact on access from subsidizing ACT pricing in rural private sector.

**2019**
1st medicine: 2 years earlier than promised – Coartem® Dispersible, developed with partner Novartis, registered by Swissmedic, becomes the first child-friendly ACT approved by a stringent regulatory authority.

**Medicines for Malaria Venture | Annual report 2019**
Global malaria mortality down by 47% from 2000

Over 230 Malaria Boxes delivered to research groups globally

Pathogen Box launched to catalyse malaria and neglected diseases drug discovery

Global malaria mortality down by 47% from 2000

Over 230 Malaria Boxes delivered to research groups globally

MMV has 50 staff members and a global network of over 375 partners

UN launches Sustainable Development Goals

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UN launches Sustainable Development Goals
Improving case management of uncomplicated malaria

Targeting unmet medical needs

MMV and partners are dedicated to the research and development of next-generation medicines needed for the regional elimination and eventual global eradication of malaria, in line with global frameworks from the World Health Organization (WHO) and the United Nations. Given the long timeline from discovery to launch of a new medicine, it is important to invest in compounds that have the potential to satisfy the unmet medical needs in malaria. These are described by two target product profiles (TPPs) published by MMV, which build on the global research agenda published by the Malaria Eradication Research Agenda (maiERA) Consultative Group on Drugs in 2017.

TPP1 defines the characteristics of a combination of drugs for the treatment of uncomplicated malaria by targeting all stages of the malaria parasite's life cycle. The ultimate goal is to shorten or simplify the treatment course, with medicines that also address emerging drug resistance. Such a combination should provide post-treatment protection for as long as possible and also reduce transmission. In the best case, it would be what is known as a single-exposure radical cure, administered as one or more doses in a single day, thus simplifying case management and helping to improve compliance.

TPP2 describes the characteristics of drugs for the protection of populations entering an area of high malaria endemicity. Ideally, these drugs are administered as a single dose repeated over a long period (monthly). This is described as single-exposure prophylaxis and would include at least one molecule with activity against the liver stage of the parasite life cycle, which precedes the blood stage. To reduce the risk of drug resistance emerging, for a given geographic area, combinations used for protection should not contain the same components as those used to cure malaria. Given the long duration of protection required for TPP2, MMV is exploring a variety of approaches, such as new formulations, prodrugs and monoclonal antibodies.

The development of a new treatment for uncomplicated malaria or a new prophylactic regimen requires the combination of at least two active drugs. MMV has defined five target candidate profiles (TCPs), corresponding to different attributes needed in the molecules that will form new combination therapies (Figure 2). TCP1 describes a candidate compound’s activity against the blood stage of the parasite life cycle, and TCP3 describes its activity in preventing relapses of malaria, caused by the hypnozoite liver stage of P. vivax and P. ovale malaria (hypnozoites can lie dormant in the liver for long periods, reactivating periodically to cause relapses). Two TCPs describe a candidate’s ability to block transmission of malaria, either by killing the malaria parasite in the human host (TCP5), or by killing the mosquitoes that carry it (TCP6). All molecules with blood-stage activity are also profiled for their potential to become new injectable treatments for severe malaria.

Central to everything is that all new molecules must be highly active against all existing resistant isolates, and be tested for their robustness against generating resistance in the future. MMV places a priority on compounds that are ‘irresistible’ in discovery, in other words those for which it is not possible to generate resistant strains in the laboratory when the compound is incubated with large numbers of malaria parasites.

Figure 2: Linking the TPPs to the TCPs
Antimicrobial resistance

Microbes evolve naturally to resist the drugs that are used to fight them. This phenomenon, known as ‘antimicrobial resistance’, threatens the public health response to many infectious diseases, including malaria. The best insurance policy against the risk of antimalarial drug resistance is to replenish the pipeline and bring new and novel-acting medicines forward, which MMV has been successfully enabling for over 20 years. Furthermore, the development of next-generation combination therapies to combat resistance (pp. 12–13, 18, 30–33), and promoting open-source approaches to identify promising drug candidates with irresistible mechanisms of action (p. 35).

How much of a threat to global health and the world's economy is antimicrobial resistance?

- Antimicrobial resistance remains a significant immediate and long-term threat to global health and the world’s economy. Currently, around 700,000 people die each year due to drug-resistant disease, and if we do not act now to minimize the further spread of resistance, the number of deaths could rise to 10 million per year by 2050. Antimicrobial resistance also poses a serious economic threat, by 2050, it could force up to 24 million people into extreme poverty, and the cost in terms of lost global productivity between now and 2050 could be as high as USD 100 trillion. It is therefore clear that without urgent action, antimicrobial resistance will continue to threaten the public health gains we have made so far.

What effect could drug resistance have on malaria control efforts?

- The success of malaria control and elimination efforts depends largely on the sustained efficacy of artemisinin-based combination therapies (ACTs). The evolution of treatment failure to ACTs in the Greater Mekong Subregion needs to be monitored closely, as well as the possible emergence of artemisinin resistance in other areas of high malaria burden, which, according to modelling studies, could kill as many as 116,000 additional people per year.

In economic terms, the predicted medical costs associated with artemisinin resistance (resulting from retreatment of clinical failures and non-artemisinin-based management of severe malaria) exceed USD 32 million per year, while productivity losses resulting from excess morbidity and mortality are estimated at USD 385 million for each year in which failing ACTs are in use as first-line treatments. However, the true impact of drug resistance on malaria control efforts is likely to vary between regions, depending on complex factors such as health system infrastructure, population dynamics and the state of each country’s economy.

How can be done to anticipate and mitigate the emergence of further drug resistance in malaria?

- Combating antimicrobial drug resistance requires a highly collaborative approach between different stakeholders, at a national and regional level. From a scientific perspective, we need to implement comprehensive surveillance studies to identify and track resistant strains, as well as monitor the therapeutic efficacy of existing treatments, using the results from these studies to inform national treatment policy and provide early warnings for treatment failures. Scientific networks such as the Asia Pacific Malaria Elimination Network are key to exchanging knowledge, building capacity, and expanding the evidence base to support regional elimination efforts. Raising political awareness is also crucial, so that recommendations from the scientific community can be implemented in a timely and sustained manner, and adequate funding mobilized at a domestic and global level.

How do you see the role of MMV in terms of open-source innovation to accelerate the development of next-generation medicines?

- MMV is one of the most established PDPs working in global health, and is therefore well placed to catalyse international research and development efforts to find effective and affordable drugs for malaria. Today, in April 2020, there is an urgent global need to identify potential drugs for the treatment of COVID-19. Several compounds from MMV’s Pandemic Response Box are currently being tested against SARS-CoV-2 – the virus responsible for COVID-19, highlighting the value of open-source libraries for the international community. Collective resources and collaborative initiatives such as these will maximize the impact of efforts to contain antimicrobial resistance and identify treatments for new diseases, while reducing costs and duplication of efforts.

Dr Stephanie Williams tells us more about the threat of antimicrobial resistance and what can be done to tackle it.

MMV attended the inaugural Global Health Security Conference, Sydney, delivering messages on the importance of epidemic preparedness, addressing the risk of antimicrobial resistance and lessons learnt from R&D partnerships like MMV.

References:
10 Cambodia, China (specifically Yunnan Province and the Guangxi Zhuang Autonomous Region), Laos, Myanmar (Burma), Thailand, and Vietnam
Beyond ACTs: next-generation therapies to counter resistance

As noted on page 11, antimicrobial resistance threatens the effective prevention and treatment of an ever-increasing range of infectious diseases, including malaria. ACTs are the first-line treatment for acute, uncomplicated malaria in approximately 80 countries. However, because they require administration over 3 days,12 patients may not always adhere to the complete treatment regimen, which can expose parasites to suboptimal doses and lead to the development of drug resistance. Several ACTs are now failing against *Plasmodium falciparum* malaria in parts of South East Asia, where both artemisinin and partner drug resistance have been identified, and most recently, markers of partial artemisinin resistance have been reported in Rwanda. If resistance to artemisinin (or partner drugs such as lumefantrine and pyronaridine) were to take hold in sub-Saharan Africa, where the malaria burden is highest, it could lead to failure of the ACTs, which would pose a major threat to malaria control and elimination efforts.

Over the last decade, MMV and partners have brought a wide range of fixed-dose, 3-day ACTs through clinical development, with a focus on making them child-friendly and affordable. These ACTs are all manufactured to international standards, with prices as low as USD 0.30 per child, or USD 0.60 per adult—well below MMV’s original optimistic goals. However, malaria is an infectious disease, and there is always the risk of resistance. In the last decade, piperaquine has joined amodiaquine and mefloquine as partner drugs for which resistance has been detected. Fortunately, to date there has been no confirmed clinical resistance to lumefantrine or pyronaridine, but this may only be a matter of time, and the malaria community needs to be ready.

Currently, MMV has two combinations being tested in Phase II studies in Africa—artefenomel-ferroquine and ganaplacide-lumefantrine. The clinical plan is to show good activity in children as young as 2 years old, with regimens varying from 1 to 3 days. In drug development, there is always a high risk of clinical failure at this stage of development, as it’s the first time the medicines are tested in their intended target population. What is important is to have other drugs in the pipeline that could be used to pair up and form new combinations. MMV and partners already have two such compounds, cipargamin and MMV048 (p. 18), and each year one or two more join this list, with Zydus Cadila’s MMV253 joining in 2019 (p. 19).

Above all, any new combination must be effective, have an acceptable safety profile, be fully active against drug-resistant parasite strains, and offer the potential for more convenient therapy.

### Table 2: Activity of MMV-supported molecules in development, 2019

<table>
<thead>
<tr>
<th>Target indication</th>
<th>MMV/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>Artefenumel (SZ439)/ferroquine (FQ)</td>
<td>MMV* (Sanofi, Monash Univ./Univ. of Nebraska/Swiss TPH)</td>
<td>Patient exploratory (Phase I)</td>
<td>Patient exploratory (Phase I)</td>
<td>Patient exploratory (Phase I)</td>
<td>Patient exploratory (Phase I)</td>
<td>Patient exploratory (Phase I)</td>
</tr>
<tr>
<td>Ganaplacide (KAF156)/lumefantrine</td>
<td>Uncomplicated malaria, potential for prophylaxis</td>
<td>Novartis</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
</tr>
<tr>
<td>Cipargamin (KAE609)</td>
<td>Uncomplicated malaria, potential for use in severe malaria</td>
<td>Zydus Cadila (AstraZeneca)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
</tr>
<tr>
<td>MMV048</td>
<td>Uncomplicated malaria, potential for prophylaxis</td>
<td>MMV* (Univ. of Cape Town)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
</tr>
<tr>
<td>M5717 (DD0496)</td>
<td>Uncomplicated malaria, potential for prophylaxis</td>
<td>Merck KGaA (Univ. of Dundee)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
</tr>
<tr>
<td>P218</td>
<td>Prophylaxis</td>
<td>Janssen (Biotec Thailand)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
</tr>
<tr>
<td>MMV253</td>
<td>Uncomplicated malaria</td>
<td>Zydus Cadila (AstraZeneca)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
</tr>
<tr>
<td>MMV533 (SAR121)</td>
<td>Uncomplicated malaria</td>
<td>MMV* (Sanofi)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
<td>Human volunteers, (Phase I)</td>
</tr>
<tr>
<td>MMV370/MMV371</td>
<td>Uncomplicated malaria, potential for prophylaxis</td>
<td>Janssen (Calibr)</td>
<td>Preclinical</td>
<td>Preclinical</td>
<td>Preclinical</td>
<td>Preclinical</td>
</tr>
<tr>
<td>MMV183</td>
<td>Uncomplicated malaria, potential for use in severe malaria</td>
<td>TropIQ (AstraZeneca)</td>
<td>Preclinical</td>
<td>Preclinical</td>
<td>Preclinical</td>
<td>Preclinical</td>
</tr>
<tr>
<td>MMV646 (LPC3210)</td>
<td>Uncomplicated malaria</td>
<td>Jacobus</td>
<td>Preclinical</td>
<td>Preclinical</td>
<td>Preclinical</td>
<td>Preclinical</td>
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<tr>
<td>INE963</td>
<td>Uncomplicated malaria</td>
<td>Novartis</td>
<td>Preclinical</td>
<td>Preclinical</td>
<td>Preclinical</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Aboguanil</td>
<td>Prophylaxis</td>
<td>Ipca</td>
<td>Preclinical</td>
<td>Preclinical</td>
<td>Preclinical</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

* MMV listed where we have assumed operational responsibility.
Front runner projects

- **Ganaplacide (KAF156)/lumefantrine (LUM-SDF)**

  Ganaplacide/lumefantrine is a novel combination currently being assessed for its potential use in acute, uncomplicated malaria. Ganaplacide is a fast-acting compound with a novel mechanism of action, capable of killing both *P. falciparum* and *P. vivax* parasites, and is active against parasites that are resistant to currently-used antimalarial drugs. Its partner lumefantrine, clears any remaining parasites (a new formulation of lumefantrine has made once-daily administration possible). Importantly, both components also have the potential to block onward transmission of parasites from humans to mosquitoes.

In 2017, MMV and Novartis initiated a Phase IIb clinical trial of ganaplacide/lumefantrine in nine countries across Africa and Asia. Results from part A of the study, in 349 adults and adolescents aged ≥12 years treated for between 1–3 days, showed rapid killing of parasites and a low rate of treatment failure. In part B of the study, the combination will be tested in children aged 2–12 years. One further study is currently planned to begin in 2020 – a paediatric study to evaluate the efficacy, safety and pharmacokinetics of ganaplacide/lumefantrine in very young children (from 6 months).

- **Artefenomel (OZ439)/ferroquine (FQ)**

  Artefenomel/FQ is also a novel combination. It consists of the fast-acting compound artefenomel, which kills most parasites in the blood and alleviates the clinical symptoms of malaria within a short timeframe, and the longer-acting compound FQ, which destroys any remaining parasites. As a single-dose treatment, artefenomel/FQ has the potential to reduce dosing frequency, thereby improving patient compliance and, crucially, slowing down the development of resistance.

In 2019, MMV took over operational responsibility from Sanofi for Phase II clinical development of artefenomel/FQ. The "FALCI" trial, a Phase IIb combination study to determine the efficacy and safety of a single dose in patients aged 6 months to 70 years, completed interim analysis in October 2019 with ~250 patients (children ≤5 years in Africa) but did not show expected efficacy results. Consequently, following review of the interim data by an independent data monitoring committee, further patient recruitment for this study was stopped. To ensure that key insights are carried forward, final results from the trial will be analysed, along with modelling and simulation data, to explore whether a two-dose or three-dose cure would have been effective, and to identify a potential new partner for FQ.
Providing treatment options for uncomplicated malaria today

Since its inception in 1999, MMV has worked with over 400 partners in 50 countries to bring forward 11 new antimalarial medicines, including five new treatments developed especially for children. However, international regulatory approval is only the first step in achieving patient access to these medicines. Before a product can be used at national level, it must first be registered by that country’s drug authority. National Malaria Control Programmes (NMCPs) consider the available scientific evidence, in conjunction with current WHO guidance, before changing their policy and reallocating finances to include a new treatment. MMW works closely with both the WHO and NMCPs to ensure that peer-reviewed evidence about its medicines informs policy and guideline changes. In addition, MMV supports post-launch studies to generate real-world safety data on new drugs, and develops innovative packaging solutions and easy-to-follow instructions to support product use at the community level.

Medicines brought forward by MMV and partners

**Coartem® Dispersible**

Coartem Dispersible (artemether-lumefantrine), developed by MMV and Novartis and approved in 2009, was the first artemisinin-based combination therapy developed specifically for children and approved by a stringent regulatory authority. It is indicated for the treatment of children weighing between 5 kg and <25 kg with acute, uncomplicated P. falciparum malaria, and quickly became the leading quality-assured dispersible product for this patient population. The development and approval of Coartem Dispersible has paved the way for WHO prequalification (WHO-PQ) of generic versions of dispersible artemether-lumefantrine by five companies, further increasing the availability and uptake of the product. Since its launch in 2009, over 390 million Coartem Dispersible treatments have been distributed to more than 50 countries, which is estimated to have saved >840,000 lives. The product is now approved in 40 malaria-endemic countries.

As part of MMV’s efforts to expand coverage to the smallest and most at-risk children, a new formulation of dispersible artemether-lumefantrine specifically for infants <5 kg is currently under development in collaboration with Novartis.

**Pyramax®**

Pyramax (pyronaridine-артесunate), developed by MMV and Shin Poong Pharmaceutical Co. Ltd., is the only ACT specifically approved by a stringent regulatory authority for the treatment of adult, uncomplicated malaria caused by both P. falciparum and P vivax, in adults and children. In 2012, Pyramax tablets were approved under the European Medicines Agency’s (EMA) Article 58 procedure, initially receiving a restrictive label due to a lack of real-world safety data to support repeat dosing, and concerns about liver safety signals. Since then, an extensive programme of post-approval, Phase IV studies in Africa have generated the evidence to support a less restrictive label, and the final study requested by the EMA completed recruitment in 2019, showing positive preliminary results. Today, Pyramax is available in both tablet (for adults and children ≥20 kg) and granule (for children from 5 kg to <20 kg) formulations, both of which are included in the WHO’s list of prequalified medicines and the Essential Medicines Lists for adults and children. Based on this strong evidence, Pyramax has been launched in 13 countries; four countries have already added it to their National Treatment Guidelines, and over 400,000 patients were treated in 2019.

In October 2019, the WHO issued an information note on Pyramax, stating that “artesunate-pyronaridine can be considered a safe and efficacious ACT for the treatment of uncomplicated malaria in adults and children weighing 5 kg and over in all malaria-endemic areas”, and stated that “in due time the Global Malaria Programme will revise the Guidelines for the Treatment of Malaria” to reflect this. This clarification from the WHO should support further uptake of this important medicine.

**Eurartesin®**

Eurartesin (dihydroartemisinin-piperaquine) is a once-daily, fixed-dose ACT developed by MMV and Alfasigma S.p.A. for the treatment of acute, uncomplicated P. falciparum malaria in adults, children and infants weighing >5 kg. It received marketing authorization from the EMA in 2011, WHO-PQ in 2015, and was added to the WHO Essential Medicines List in 2017. The approval of Eurartesin led to the development and WHO prequalification of the first generic version of dihydroartemisinin-piperaquine – available in two formulations, including the first dispersible paediatric formulation – in 2019. Alfasigma S.p.A. is currently developing its own paediatric formulation that, if approved, would further increase the child-friendly treatment options for endemic countries.

**ASAQ Winthrop® and ASMO**

In addition, MMV has taken on the access stewardship of two additional ACTs, artesunate-amodiaquine (ASAQ) and artesunate-mefloquine (ASMO), originally developed by the Drugs for Neglected Diseases initiative and partners, which includes support for product adoption and use in endemic countries. This brings the total number of quality-assured ACTs in MMV’s portfolio to five, two of which are designed specifically for use in children. MMV is now engaging with multiple industry partners to increase access to these vital ACTs. Over the past 20 years, the treatment landscape for uncomplicated malaria has evolved dramatically, thanks largely to the efforts of MMV and partners.

On World Malaria Day, the Swiss Agency for Development and Cooperation and the Swiss Malaria Group hosted an event to reflect on 20 years of successful Swiss collaborations for new antimalarial medicines, such as Coartem Dispersible, and to discuss the way forward for malaria elimination.
Dr Bernhards Ogutu  
Chief Research Officer,  
Kenya Medical Research Institute

**INTERVIEW**

MMV and partners are implementing two operational feasibility studies involving MFTs. Following completion of an initial pilot study in Burkina Faso, a second study is now underway; and in Kenya, a pilot study is expected to begin in 2020. It is hoped that results from these studies will answer questions about the feasibility and logistics of MFT and eventually support broader policy changes in endemic countries.

Dr Bernhards Ogutu tells us about the case management of uncomplicated malaria in Kenya, and the potential value of MFTs.

**Multiple first-line therapy options**

Diagnostic testing and prompt treatment – within 24 hours of onset – is required for the effective case management of malaria. In line with WHO recommendations, most countries have adopted ACTs, typically administered over 3 days, as the first-line treatment for acute, uncomplicated malaria. However, sustainable treatment strategies are needed to protect these valuable ACTs against the threat of resistance (alternatives to artemisinin derivatives are not expected to enter the market for several years). One such strategy is the use of multiple first-line therapies (MFTs), which are made available in both the public and private sectors for physicians to choose from. By deploying multiple therapies – compared with only a single therapy – across the population, resistance to ACTs may develop at a slower rate.

MMV and partners are implementing two operational feasibility studies involving MFTs. Following completion of an initial pilot study in Burkina Faso, a second study is now underway; and in Kenya, a pilot study is expected to begin in 2020.

It is hoped that results from these studies will answer questions about the feasibility and logistics of MFT and eventually support broader policy changes in endemic countries.

**How has the treatment landscape for uncomplicated malaria changed in Kenya over the last 20 years?**

- The malaria treatment landscape in Kenya has changed considerably. The transition from monotherapy with a short duration of post-treatment protection. This means that if a patient shows symptoms of infection after completing a 3-day course of artemether-lumefantrine, physicians may perceive that the drug is not effective, and might switch to a more familiar, but outdated, treatment. If MFTs are available, physicians can choose another combination therapy and stay within the guidelines.

**How has MMV helped to improve the case management of uncomplicated malaria in Kenya?**

- By bringing together various stakeholders from both endemic and non-endemic countries, MMV has changed the way new antimalarial drugs are developed. For paediatric medicines in particular, MMV has shifted the whole paradigm by establishing partnerships to bring forward palatable, child-friendly formulations, such as Coartem Dispersible. Without MMV, such progress would have been very difficult to achieve. In Kenya, we are now starting to explore MFT pilots in partnership with the public and private sectors. MMV’s support in helping us prepare for an MFT feasibility study has been very valuable, and we look forward to seeing whether this new approach could help to improve the case management of malaria in Kenya.

**What are the advantages of having MFTs available in malaria-endemic countries?**

- The biggest advantage of MFTs is that they can reduce the risk of resistance to currently available ACTs. MFTs can also prevent the use of outdated drugs. For example, artemether-lumefantrine, which is the first-line treatment in Kenya, is effective at clearing the blood-stage infection, but only provides a short duration of post-treatment protection. This means that if a patient shows symptoms of infection after completing a 3-day course of artemether-lumefantrine, physicians may perceive that the drug is not effective, and might switch to a more familiar, but outdated, treatment. If MFTs are available, physicians can choose another combination therapy and stay within the guidelines.

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23 Other research groups are exploring the potential of Triple ACTs (TACTs) to slow the spread of resistance.
26 In collaboration with Prof. Gilbert Kokwaro, Director, Institute of Healthcare Management, Strathmore Business School, Nairobi, Kenya. Pyronaridine-artesunate is currently under consideration for inclusion in the Kenyan National Treatment Guidelines.
27 Pyronaridine-artesunate is currently under consideration for inclusion in the Kenyan National Treatment Guidelines.
28 Coartem Dispersible is a cherry-flavoured formulation that dissolves in 10 ml of water.

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“...MMV has shifted the whole paradigm by establishing partnerships to bring forward palatable, child-friendly formulations...”
Malaria in pregnancy

In 2018 alone, 11 million pregnancies in sub-Saharan Africa were exposed to malaria, resulting in high levels of maternal anaemia and 872,000 low-birthweight babies.31 Pregnant women infected with malaria are at increased risk of cerebral malaria and severe anaemia, as well as outcomes such as miscarriage, premature delivery and low-birthweight babies.32

To protect pregnant women, the WHO recommends intermittent preventative treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP), starting as early as possible in the second trimester. Beyond SP, there are currently no alternative options for IPTp, which is especially problematic for pregnant women living in areas of SP resistance, and for HIV-positive pregnant women who are not eligible to receive SP. Despite increased mobilization from countries in recent years, only 31% of eligible pregnant women receive the recommended three doses.33 For pregnant women who become infected with malaria during their second or third trimester, the WHO recommends ACTs, which are the first-line treatment for patients with uncomplicated malaria. However, for women in their first trimester of pregnancy, only the older antimalarial, quinine, together with the antibiotic, clindamycin, is currently recommended by the WHO. This is despite the availability of four generic versions of artemether-lumefantrine now prequalified by the WHO for use in all trimesters of pregnancy, and the removal of the contraindication for use in pregnancy from the US prescribing information of Coartem® (artemether-lumefantrine) tablets (as of August 2019).34

New medicines that can be used to treat and prevent malaria in all stages of pregnancy are therefore urgently needed, but drug development is a long and complicated process, particularly when it involves pregnant women.35 Women of child-bearing age are systematically excluded from clinical trials to protect the potential mother and foetus, but ironically this prevents the generation of data to assess the risks and benefits in pregnant women. As a result, most drugs become available to pregnant women 5–10 years later than for non-pregnant women – only after completion of post-approval pregnancy registries or other studies. In this timeframe, drug resistance can develop, further limiting the options available to pregnant women. Furthermore, the paucity of data can lead to uninformed decision-making by practitioners and patients, who might be taking medicines, nonetheless.

Increasing options for pregnant women

For several years, MMV has been committed to providing informed therapeutic choices for malaria treatment and prevention across all genders and age categories, including pregnant women. As part of this commitment, MMV collaborated with Pfizer between 2013 and 2016 to investigate the safety and efficacy of azithromycin plus chloroquine (AZ+CQ) as an alternative to SP for IPTp in an open-label, Phase III study in countries where SP is the current standard of care, but resistance is evident. Although AZ+CQ did not show any clinical benefit, the study highlighted the significant protective benefit of IPTp with SP; in conjunction with controlled usage of insecticide-treated bed nets – a finding that supported the WHO’s ongoing recommendations for IPTp using SP. In addition, unexpected tolerability findings in the AZ+CQ arm of this study, such as vomiting, underscored the need for new medications for this population.36

While new drugs are being discovered and developed, MMV is working with partners to fill the data gap on the use of existing antimalarial drugs in pregnancy. MMV and the Liverpool School of Tropical Medicine, UK, recently completed an analysis of retrospective and prospective data from pregnant women exposed to dihydroartemisinin-piperaquine (DHA-PQP) as compared to quinine, during their first trimester in Indonesia.37 No congenital abnormalities were found and the safety profile of DHA-PQP was similar to that of quinine. In collaboration with the MMV is the London School of Hygiene & Tropical Medicine, UK, MMV is also evaluating the cardiac safety of a single course of IPTp with DHA-PQP in Tanzania. It is hoped that the findings from these studies will generate the evidence needed to increase antimalarial treatment options for pregnant women. Lastly, to help address the issue of low IPTp uptake, MMV is working with industry partners, Unitaid, and the WHO to ensure an adequate supply of quality SP for use in IPTp.

In 2020, recognizing the need to continue the important efforts to scale-up IPTp, the RBM Malaria in Pregnancy Working Group, which includes MMV, will launch the ‘Speed-up, Scale-up’ campaign. The aim is to rally key stakeholders to bring this lifesaving intervention to all the women who need it.
In 2019, MMV laid the foundations for a new initiative – Malaria in Mothers and Babies (MiMBa, meaning ‘pregnancy’ in the Swahili language) – which aims to address the needs of pregnant women and their newborn babies affected by malaria. Dr Wiweka Kaszubska tells us more.

**How did the MiMBa initiative start out?**

It was really a spontaneous movement among different experts from the MMV team, who started to ask what more we could do to ensure equitable access to medicines by pregnant women with malaria. We recognized that malaria elimination will not fully succeed without the intentional inclusion of women who are, or might become, pregnant. Even in the absence of supportive epidemiological data, it is easy to imagine that in Africa, pregnant women must represent a large proportion of the population that carry malaria parasites. Currently, too few medicines can be safely used by pregnant women, particularly in the first trimester, and by women who might become pregnant. We formalized the MiMBa initiative and extended it to include women who are breastfeeding, and babies, thereby covering the whole continuum.

**What does the MiMBa initiative aim to achieve?**

In the near-term, we aim to fill data gaps on the use of current antimalarial medicines, which relate mostly to safety, but also to efficacy. In many cases, we don’t have the pharmacokinetic data to support the doses of currently-used antimalarials, which might need to be adjusted in women who are pregnant or who are breastfeeding. There are also gaps on how to increase the coverage of antimalarials for these populations, so our APM35 team will conduct relevant operational research. As we develop new antimalarial medicines for the general population, the R&D team has the challenge of collecting data to help policymakers evaluate the risk-benefit profile of medicines for use in pregnant or lactating women.

**What can MMV do to bring forward new medicines for pregnant women and babies?**

MMV is operating within a broader movement rooted in gender equity to address gaps for pregnant women. Recognizing that gaps in adequately tolerated and effective therapies exist across all diseases, the US National Institutes of Health established a global task force (PRGLAC), which identifies the gaps in knowledge and research, and proposes recommendations that we intend to follow. A similar effort is underway by the European Innovative Medicines Initiative’s ConcePTION project. MMV’s contribution is to bring malaria, a disease of the developing world, into this global movement.

MMV’s drug discovery strategy already includes an early focus on admitting drug candidates to the development portfolio that have a promising safety profile for future use in pregnancy. To strengthen our approach to non-clinical studies, we plan to work even closer with our ESAC to select the most predictive in vitro and laboratory models, standardize interpretation of data, and ensure consistency in ranking and prioritization of compounds with a favourable profile. MMV and partners are also establishing modelling approaches to predict if a compound is likely to cross the mother’s placenta, and how much of it might be found in her breast milk. Based on supportive data, it may be possible to conduct pharmacokinetic studies in pregnant women in parallel to Phase III development of a new drug, giving patients and physicians early and reliable information regarding its potential use during pregnancy.

**Has the MiMBa initiative led to any specific projects yet?**

We are establishing a pregnancy registry with the Liverpool School of Tropical Medicine, UK, covering several malaria-endemic countries in Africa. This multicentre, prospective, observational study will provide insights on the safety profile of a range of ACTs used during pregnancy in a real-world setting. We plan to collect data on the health of mothers and babies in the next few years, to support evaluation of the benefit-risk profiles of selected ACTs and inform decision-making on their use, particularly in the first trimester of pregnancy.

With our long-standing partner, Novartis, MMV is also developing what could become the first medicine for the treatment of acute, uncomplicated malaria in neonates weighing under 5 kg. This is a new ratio of artemether plus lumefantrine (the components of Coartem Dispersible, p. 14), which we hope will enter clinical testing in 2021.
Any candidate compound or combination in the pipeline has the potential to fail at any stage of clinical development due to reasons of formulation, safety, tolerability or efficacy. Even in the post-approval setting, medicines can fail due to resistance in the field. To mitigate against this risk, MMV strives to continuously maintain and enrich the malaria drug development pipeline with compounds that meet its target candidate and target product profiles (p.10). In 2019, several of MMV’s portfolio compounds progressed in their clinical development.

**Cipargamin**

Cipargamin (KAE609), developed by Novartis in collaboration with MMV and with financial and technical support from the Wellcome Trust, has the potential to become part of a fast-acting combination treatment for uncomplicated malaria, or a next-generation treatment for severe malaria. Cipargamin targets a cell membrane channel in the parasite, the first validated new molecular target for severe malaria. Cipargamin rapidly cleared parasites from the blood of adults with uncomplicated *P. falciparum* or *P. vivax* malaria. A subsequent study demonstrated the compound’s longevity in the blood, where a 75 mg dose resulted in blood concentrations above the level needed to kill parasites for over 8 days. In addition to its asexual blood-stage activity, cipargamin also has the potential to block transmission of malaria. Potential combination partners for cipargamin are being evaluated, and Phase I testing of a new formulation of cipargamin for intravenous use in severe malaria is planned for 2020.

**MMV048**

MMV048 was discovered and developed by an international team led by scientists at the University of Cape Town, South Africa, and was the first antimalarial candidate compound to enter a Phase I study in Africa. MMV048, which works by inhibiting a key enzyme in the parasite, is active against the asexual blood stage and liver stage of the parasite life cycle, and thus it could be used for both treatment and prophylaxis. MMV048 also kills gametocytes, which means it has the potential for transmission blocking. An 80 mg dose of MMV048 is predicted to stay in the blood above the concentration needed to kill parasites for over 8 days, indicating good longevity. Non-clinical studies have indicated that MMV048 is not a suitable candidate for use in pregnancy; however, it still holds promise for use in adults, non-pregnant women and children. A Phase IIa study in Ethiopia to further explore the efficacy of the compound in patients with *P. falciparum* and *P. vivax* malaria is on hold but should resume once the COVID-19 crisis has been brought under control.

**M5717**

M5717 (formerly DDD498), in development with Merck KGaA, shows activity against all stages of the parasite life cycle (except for the dormant liver stage of *P. vivax* malaria). As such, this compound has the potential to both treat and protect at-risk populations. M5717 has a novel mechanism of action, targeting the protein-making machinery of the malaria parasite. In a Phase I study in 2018, the compound was shown to be well tolerated, and an 800 mg dose of M5717 completely cleared a blood-stage infection in a volunteer infection study (VIS) – a type of study in which healthy volunteers are injected with a low number of drug-sensitive sporozoites before receiving an experimental drug 8 days later to assess its blood-stage activity. The next stage for M5717 is a VIS to evaluate its prophylactic activity in humans. In parallel, ongoing activities are being conducted to select the best combination partner and to start combination studies in humans.

**P218**

P218 is a potential long-acting, single-administration, injectable drug for prophylaxis that is being developed in collaboration with Janssen and is currently in Phase I development (p. 33). The compound acts via a clinically validated pathway and has shown efficacy against known drug-resistant malaria parasites. The prophylactic activity of P218 has been demonstrated using a variant of the VIS model, in which healthy volunteers receive an experimental drug before being injected with a low number of drug-sensitive sporozoites. These studies enable MMV and partners to assess the potential of experimental drugs, such as P218, to protect against an infection taking hold in humans. If successful, P218 in its long-acting, injectable formulation could provide protection with a low-frequency dosing schedule, making it a valuable tool for malaria prophylaxis in highly endemic areas.

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39 Originally discovered as part of a Novartis-led consortium, funded by MMV, the Wellcome Trust and the Singapore Economic Development Board in collaboration with the Swiss Tropical and Public Health Institute.


41 As shown by data from the standard membrane feeding assay, a laboratory model for assessing the transmission-blocking potential of candidate compounds.

42 Active against the liver stage of uncomplicated *P. falciparum* and *P. vivax* malaria only; not active against relapsing *P. vivax* malaria (liver-stage hypnozoites).
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 (p. 30). MMV253 has the potential, when combined with the right partner, to become a single-exposure, blood-stage treatment for acute, uncomplicated *P. falciparum* and *P. vivax* malaria. MMV253 has shown a good safety profile in both non-clinical toxicology studies and Phase I studies in humans, a low susceptibility to resistance, and a profile that suggests it may eventually be suitable for use in pregnancy. The next step for this promising molecule will be to develop a combination strategy for further clinical development.

**New drug candidates**

MMV’s current portfolio includes three preclinical candidates: MMV533 (transferred from Sanofi), 43 two prodrugs44 of atovaquone for use in a potential injectable drug for prophylaxis (MMV370/MMV371; one to be selected to enter GLP-compliant preclinical safety studies45), and a novel compound from GSK, GSK701.46 Furthermore, in 2019, MMV’s Expert Scientific Advisory Committee47 recommended three new candidates for progression to preclinical testing: MMV183, MMV646 and INE963 (pp. 36–37), each with its own unique and exciting profile. Together, these candidates represent MMV’s strongest and most diverse portfolio to date. Behind these in the pipeline are 33 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.

“MMV strives to continuously maintain and enrich the malaria drug development pipeline with compounds that meet its target candidate and target product profiles.”
Protecting those most at risk

Children under the age of 5, who have developed little or limited immunity to malaria, are most at risk of the disease. In 2018, this group accounted for 67% of all malaria deaths worldwide, most of which occurred in sub-Saharan Africa.1 In the absence of an effective vaccine to protect children against malaria, the World Health Organization (WHO) recommends seasonal malaria chemoprevention (SMC), whereby full antimalarial treatment courses are administered to children at regular intervals during periods of high malaria transmission (typically the rainy season, which lasts 3–4 months). MMV and its partners are working hard to maximize supply security and access to currently available medicines for SMC, to support the generation of evidence that could justify an age-range expansion of SMC, and to develop new alternatives that could expand the geographical reach of SMC to other areas of seasonal transmission in Africa.

Seasonal malaria chemoprevention (SMC)

In 2012, the WHO recommended monthly administration of the medicine sulfadoxine-pyrimethamine plus amodiaquine (SPAQ) for SMC in the Sahel region of sub-Saharan Africa. In clinical trials, SPAQ has been shown to reduce cases of uncomplicated and severe malaria by 75% in children under 5,2 and post-implementation data from Mali and Burkina Faso have shown it reduces the chance of testing positive for malaria during the season by 44–62%.3,4 However, coverage is not universal. In 2018, about 12 million children who could have benefited from SMC were not covered,5 so continued efforts are needed to reach more children.

MMV’s partner Fosun Pharma is the only WHO-prequalified supplier of SPAQ. To increase the number of quality-assured suppliers, MMV has been supporting a second manufacturer, S Kant Healthcare Ltd. (India) to develop a second child-friendly, dispersible SPAQ product (Supyra®). In July 2018, S Kant submitted a dossier to the WHO prequalification (PQ) programme,6 and subsequently to the Global Fund Expert Review Panel (ERP) in September 2018. The ERP issued a positive opinion in February 2019, allowing countries to purchase Supyra with international donor funds until February 2020, while the WHO-PQ review was ongoing.7 Market authorization of Supyra has now been achieved in two countries and review is ongoing in a further five.8 Since the launch of SMC in 2014, the number of protected children has increased from 3 million in 2015 to over 20 million in 2019. This dramatic scale-up has been achieved in part by the distribution of 96 million treatment courses of SPAQ (Fosun Pharma and S Kant products combined) in 13 countries in 2019, bringing the total number of courses distributed since 2014 to 357 million.

The WHO recommends SMC in children aged 3–59 months. However, data from Senegal, which has implemented SMC in children up to 10 years, suggest that SMC is as effective, and cost-effective, in the higher age group (5–10 years) as in children under 5. As a result, four countries9 are now considering increasing the age range for SMC. MMV’s SEAMACE9 programme will explore ways to expand coverage of SMC in the coming years, by extending the target age range, expanding geographic coverage within the Sahel, and increasing the duration of coverage where warranted by local transmission patterns (from 3–4 to 3–5 months). Given the threat of sulfadoxine-pyrimethamine (SP) resistance in eastern and southern Africa, MMV also intends to develop new combinations of existing antimalarials that can provide long-duration protection, including intramuscular injectable formulations of prodrugs10 (p. 33), as well as new therapies based on monoclonal antibody technology.11

3 http://www.who.int/malaria/areas/preventive_therapies/children/en/
5 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”.
6 WHO-PQ for S Kant’s SPAQ is targeted for year-end 2020.
7 Registered in Nigeria and Cameroon; review ongoing in Guinea, Ghana, Niger, Burkina Faso and Mali.
9 SEAMACE: Seasonal Malaria Chemoprevention Extension.
10 Prodrug: a precursor of a drug that must undergo chemical conversion by metabolic processes in the body before becoming an active pharmacological agent.
11 This was the subject of a recent review paper authored by a team of MMV’s in-house scientists: Macintyre F et al. “Injectable anti-malarials revisited: discovery and development of new agents to protect against malaria.” Malar J 17, 402 (2018).
Dr André-Marie Tchouatieu tells us about the progress and challenges of implementing SMC, and MMV’s future plans to increase its impact.

Since the WHO issued its SMC recommendation in 2012, what kind of impact has it had on the Sahel region of Africa?

In most countries that have implemented SMC, malaria incidence initially reduced by 25–60%, and malaria-related mortality by 40–45%. The intervention is therefore having a significant protective effect against uncomplicated and severe malaria. This is great news, but we will have to confirm these reductions over the coming years, and during the 2020 COVID-19 pandemic in particular. Senegal, Burkina Faso and Ghana are among the countries that have seen the most significant benefits from SMC so far, and we hope that other countries in the region will benefit as we look to increase SMC coverage. It’s really important that we apply robust and consistent methodology to assess the impact of SMC on the burden of malaria in the Sahel region, and evaluate its benefits continuously.

How are countries mobilizing national resources to increase uptake of SMC?

Some countries are seeking financial support from the World Bank and other regional banks to complement the funding they receive through multinational mechanisms such as the Global Fund and the US President’s Malaria Initiative. In addition, governments in some countries, such as Mali and Ghana, are increasingly contributing towards SMC campaigns and allocating more of their malaria funds towards SMC. However, the proportion of resources that come from national sources is still negligible, and most countries are largely dependent on international donor funding.

What are the logistical challenges associated with implementing an SMC campaign?

In the early days of implementation, forecasting the supply of SMC was a major challenge as it was based on census data that were often old and inaccurate. With updates to census data, countries are now much better able to predict their SMC supply needs. Social and political migration in some countries also makes forecasting difficult. Countries generally have an extra 10% stock of SPAQ as a buffer to cover any additional needs, but thanks to improved coordination between countries, rapid movement of stock from areas of low to high demand is now possible.

Compliance to SMC is also a challenge. The first dose of SPAQ is administered by a healthcare worker, but ensuring adherence to the second and third doses of AQ alone, which are usually given by caregivers (parents or guardians), is challenging (see pp. 22–23 for one solution). Supervised administration of the full course of SMC would be beneficial but would also increase costs. Several countries are currently exploring this option.

How has MMV helped to diversify the supplier base for SPAQ?

Only one WHO-prequalified, child-friendly SPAQ product is currently available, and so MMV is supporting a second supplier, S Kant Healthcare, to bring forward a new child-friendly, dispersible formulation. However, demand for SMC is likely to increase in the coming years due to the extension of the age range to include children up to 10 years of age, and an increased duration of coverage (up to 5 months based on changing epidemiological patterns). Ensuring a steady supply of SPAQ will therefore be crucial.

What is MMV’s mid- to long-term strategy for SMC?

Should the efficacy of SPAQ be compromised by resistance, new medicines will be needed. To increase the options for SMC, MMV is looking at new molecules, as well as repurposing existing antimalarial medicines. While exploring possible alternatives to SPAQ, we are keeping a close eye on the cost of a potential new product and trying to keep it within a similar price range as the currently approved medicines. Last year, we tested a new co-formulation of atovaquone-proguanil and amodiaquine in a drug-drug interaction study, which has the potential to achieve the same preventative efficacy as SPAQ. Unfortunately, this combination presented an unacceptable safety risk in healthy volunteers and the study was stopped.

SMC is classified as a protective intervention aimed at decreasing the number of malaria cases and deaths. However, in the long run, MMV would like to complement SMC with transmission-blocking interventions that can be administered either before or at the same time as SMC, thus contributing to an overall reduction in malaria in the community. One possible avenue could include the addition of endectocides (e.g. ivermectin), which kill mosquitoes, in combination with SPAQ; another approach could be to add a low dose of primaquine to kill gametocytes (the parasite stage that causes transmission from infected humans to mosquitoes). These approaches could help reduce rates of re-infection significantly in areas of high transmission.

Ensuring a steady supply of SPAQ will therefore be crucial.

With SMC:

- Malaria incidence reduced by 25–60%
- Malaria-related mortality reduced by 40–45%
Drocas Dako knows how to multitask. During Mali’s seasonal malaria chemoprevention campaign, she’s out of the door by 7 am to distribute free pills that protect children from malaria. She goes from one household to the next, carrying her baby on her back.

At one of the first homes, Drocas is welcomed with friendly greetings and chatter as she and the household’s grandmother, Assitar, collect the young children and sit down together in the shade of a nearby tree.

Thinking back to the training she received from a nurse at the closest health clinic, Drocas administers the pills to a 4-year-old boy, Alou, and speaks kindly as she reminds Assitar of the importance of checking off on Alou’s SMC card that the second and third doses were indeed given later at home.

That afternoon, Drocas emerges from visiting another household in the Segou region and makes a mark with chalk next to the home’s door to signal that she has visited the house and distributed medicine, as is the custom during SMC campaigns. Drocas managed to reach all six of the eligible children living there.

During the first campaign cycle in July, Drocas reminded Assitar and other caregivers that she would be back almost exactly one month later to administer another dose and would return again in both September and October.

For young children in Mali and other countries across Africa’s Sahel region, Drocas is a life saver.

“During Mali’s seasonal malaria chemoprevention (SMC) campaign, she’s out of the door by 7 am to distribute free pills that protect children from malaria.”
Karotumay holds her son, Bedy, age 2, and the card that shows he has just received an antimalarial through Mali’s SMC campaign. As a mother of six, she knows the importance of protecting children from malaria. “When children get malaria, they vomit and have such a bad fever that they can convulse and die. It’s very serious and treatment at the health centre can be very expensive,” says Karotumay. “In the past, Bedy’s older sister and brothers received SMC to prevent malaria. I know it works.”
Scaling up access to life-saving interventions for severe malaria

In 2018, there were an estimated 405,000 deaths from malaria worldwide, the overwhelming majority of which occurred in Africa. Although the risk of death due to mild, uncomplicated malaria is low, if left untreated or inadequately treated in individuals with insufficient immunity, the disease can progress within a few hours to severe malaria – a life-threatening condition characterized by high levels of parasitaemia and vital organ dysfunction. The symptoms of severe malaria include anaemia, hypoglycaemia, respiratory distress, convulsions and coma, which present significant challenges for physicians and healthcare systems. Urgent and aggressive treatment is critical if severe malaria is confirmed, yet in many endemic areas, access to diagnostic and therapeutic tools is limited.

Since 2011, the World Health Organization (WHO) has recommended injectable artesunate for the treatment of severe malaria in preference to quinine or artemether, due to its superior efficacy. The WHO also recommends the use of artesunate rectal capsules as a pre-referral emergency intervention in children under 6 years of age presenting with severe malaria symptoms, in remote areas where comprehensive treatment and care cannot immediately be provided. MMV and partners are working hard to increase access to quality-assured versions of these medicines to help improve the case management of severe malaria, and ultimately reduce mortality rates.

Injectable artesunate: improving treatment outcomes

Artesun®, developed by Fosun Pharma, was the first injectable artesunate product to receive WHO-prequalification (PQ), with the support of MMV. Since its approval in 2010, the use of Artesun has been widespread, having been approved in 33 malaria-endemic countries. To increase the security and stability of global supply over the long term, MMV is supporting additional manufacturers to seek WHO-PQ for their injectable artesunate products. In December 2018, Ipca Laboratories achieved WHO-PQ for its product, Larinate® 60 mg. With MMV’s support, Larinate 60 has now been registered and launched in 12 countries. As a result, a total of 168 million vials of injectable artesunate have been distributed to date, estimated to have saved the lives of more than one million additional children. Artesunate rectal capsules after 4–6 months in areas where the ambient temperature is usually above 30°C. As this represents an additional logistical burden for countries, MMV and partners are exploring options to generate real-world data on the condition of artesunate rectal capsules after 4–6 months in areas where the ambient temperature is usually above 30°C. As this represents an additional logistical burden for countries, MMV and partners are exploring options to generate real-world data on the condition of artesunate rectal capsules returned from the field, which may support an amendment of the current guidance.

Alongside securing a quality-assured supply of injectable artesunate, MMV is taking steps to increase uptake in endemic countries. Given the importance of providing healthcare workers with easy-to-understand information on product administration, MMV has worked closely with public health partners to develop training materials for healthcare workers (now available in four languages). Nearly two dozen countries have adopted these materials, incorporating them into their national training programmes. Managing severe malaria during pregnancy is particularly challenging, so MMV is working with National Malaria Control Programmes (NMCPs) in five countries to identify and help address gaps in the management of severe malaria during pregnancy. In 2017, MMV launched the ‘Severe Malaria Observatory’, a knowledge-sharing platform and repository of information on severe malaria for the global community, which is currently receiving over 8,000 hits per month (p. 25).

In October 2019, MMV and partners convened a global stakeholder meeting to share experiences and improve the ‘continuum of care’ for severe malaria – artesunate rectal capsules, injectable artesunate, followed by a full course of artemisinin-based combination therapy (ACT) – from the community to a referral healthcare facility. One of the challenges discussed was the WHO guidance to replace artesunate rectal capsules after 4–6 months in areas where the ambient temperature is usually above 30°C. As this represents an additional logistical burden for countries, MMV and partners are exploring options to generate real-world data on the condition of artesunate rectal capsules returned from the field, which may support an amendment of the current guidance.
Artesunate rectal capsules: the pre-referral intervention that buys time to save lives

Time is of the essence when treating severe malaria, as complications can develop rapidly and progress to death within a matter of hours. For children aged 6 months to 6 years living in remote settings, pre-referral administration of artesunate rectal capsules can buy valuable time until injectable artesunate can be administered at the nearest healthcare facility. Although the WHO has recommended the use of artesunate rectal capsules for the management of severe malaria since 2005, until recently, no WHO-prequalified product has been available, limiting its use and denying millions of children access to its benefits.

Supported by grants from Unitaid, MMV has worked with two industry partners since 2013 to bring 100 mg artesunate rectal capsules to market. Both manufacturers’ products achieved WHO-PQ in 2018, enabling countries to procure these life-saving products – Artecap™ (Strides Pharma Science Ltd) and Artesunate Rectocaps (Cipla Ltd) – using donor funds. These products are currently registered in 16 countries in sub-Saharan Africa, and a total of 3.2 million capsules have been delivered to date. Importantly, more than 90% of the capsules procured by the three largest international buyers – The Global Fund, US President’s Malaria Initiative and UNICEF – are now sourced from both MMV-supported manufacturers that supply these WHO-prequalified products.

MMV is continuing its efforts to achieve new country registrations, expand the delivery of artesunate rectal capsules and provide community-level education to increase uptake. For example, MMV and partners have initiated the RASIEC study in Malawi to evaluate the impact of introducing an information, education and communication toolkit to train community health workers on the use of artesunate rectal capsules. In 2019, MMV continued implementation of the MAMaZ Against Malaria (MAM) project to increase access to the capsules in rural areas of Zambia. In the pilot, the project had a great impact in this highly malaria-prevalent region, reducing malaria mortality in children under 6 years by 96%. Based on the success of the pilot, this project has been scaled up with support from MMV and expanded to five districts in Zambia. Furthermore, the National Malaria Elimination Centre and Zambian Ministry of Health have agreed to scale-up use of artesunate rectal capsules at the community level, with the aim of making it available nationwide.

As part of the Community Access to Rectal Artesunate for Malaria (CARA-MAL) project, funded by Unitaid and led by the Clinton Health Access Initiative (CHAI), MMV is supporting the introduction of quality-assured rectal artesunate capsules and ensuring community training on their correct use, as part of a continuum of care for severe malaria. The project is focused on three high-burden countries – Democratic Republic of the Congo (DRC), Nigeria and Uganda – and is currently piloting community case management initiatives (see N’Simba’s story, p. 27). In addition, multi-country observational research is being conducted to identify the operational and health system-related factors affecting the introduction of artesunate rectal capsules. During a Global Severe Malaria Stakeholder meeting held in Abuja, Nigeria in October 2019, 19 countries shared their experience of rolling out artesunate rectal capsules within their health systems to improve the continuum of severe malaria care from community to referral facility levels. This was the first meeting convened on severe malaria case management, building on stakeholder meetings focused on injectable artesunate and artesunate rectal capsules in 2011 and 2016, respectively.

Severe Malaria Observatory

In May 2017, MMV launched the Severe Malaria Observatory (SMO) – a repository of information on severe malaria and its management. Created by and for the global malaria community, the platform shares knowledge, experiences and treatment guidance relating to severe malaria (the site houses numerous reports and surveys), thereby deepening global understanding of, and expertise in, the disease.

In particular, the observatory aims to:

- disseminate best practices, toolkits, market information, guidelines, projects, outcomes, etc.;
- highlight the need for continuous research and capacity building;
- increase visibility and coordination of ongoing initiatives to address severe malaria.

As of late 2019, the platform was, on average, receiving more than 8,000 visits per month with the majority from African stakeholders. Peer-reviewed articles, new reports and surveys are regularly uploaded to the site (most recently, from Liberia and DRC), making SMO a widely recognized source of information on severe malaria.

www.severemalaria.org
Prof. Eric Sompwe Mukomena tells us about some of the challenges of severe malaria case management in his country.

Could you tell us about your national strategy for improving the case management of severe malaria in DRC?

- DRC has a high burden of malaria, with over 95% of the population living in areas of high transmission. Following on from its 2013–2015 strategy, the NMCP developed a new National Malaria Control Strategic Plan (NSP) for 2016 to 2020. The overall objective of this new strategy is to reduce malaria morbidity and mortality in the DRC by 40% compared with 2015; we are, however, unlikely to reach this ambitious target. For the treatment of severe malaria, the NSP recommends injectable artesunate or, if unavailable, intramuscular artemether or intravenous quinine. Pre-referral intervention with artesunate rectal capsules at a peripheral level is national policy, although roll-out of training for health workers and commodities is still ongoing.

- Despite improved coverage of malaria interventions in recent years, access to medicines, lack of funding and infrastructure challenges continue to be major obstacles for the case management of severe malaria in rural settings. As quinine is cheaper and has been the treatment of choice for many decades, it is still being used to treat severe malaria in certain parts of the country – even though it is less effective than injectable artesunate. For artesunate rectal capsules, there are knowledge gaps that prevent effective administration of the intervention, and sometimes there is just not enough supply of medicines. In some areas, patients aged 6 years and above are receiving artesunate rectal capsules, although WHO and national guidelines do not recommend them for this age group. Lastly, seeking treatment in the private sector is common in the DRC, and we cannot always ensure that private facilities are adhering to our national policies and prescribing quality-assured medicines.

What more can be done to improve case management of severe malaria in DRC?

- We need to advocate for more funding to ensure an adequate supply of quality-assured treatments for severe malaria (between 2016 and 2018, financial contributions from DRC’s three biggest donors fell by 27%). Our current priorities are training and supervision of health workers, especially in regard to pre-referral intervention, and expanding referral centres and community care sites. Alongside donor funding, we also need to mobilize government funding for severe malaria care, especially for people that currently don’t have access, and improve the integration of public–private health services to streamline care aligned to national and international guidelines. In particular, we need to do much more to improve malaria outcomes in pregnancy.

What is your experience of working with MMV?

- MMV-supported products have made a major contribution in terms of reducing the burden of severe malaria in DRC, and we welcome the diversified supply base of both injectable and rectal artesunate. Through the CARAMAL project, we are currently benefiting from the introduction of artesunate rectal capsules, made available by MMV-supported manufacturers, as well as the introduction of artesunate rectal capsules, made available by MMV-supported manufacturers, as well as community training on their correct use. We expect to identify the key gaps in our current system of integrated community case management, which in turn will help us ensure that artesunate rectal capsules are an effective part of a continuum of care – right from the community level up to a referral healthcare facility.

12 The health system in DRC has three levels: central, intermediate, and peripheral. The peripheral level is comprised of communities, health facilities, general referral hospitals and health zones.

13 Health workers in DRC work at the community level and carry out health promotion and community mobilization, and they also provide diagnosis, treatment and referral services for selected conditions, which includes administration of artesunate rectal capsules.


15 Integrated Community Case Management (ICCM) aims to provide timely and effective treatment of malaria, pneumonia and diarrhoea to populations with limited access to facility-based health care providers, and especially to children under 5. Source: WHO (2016) ‘Integrated community case management of malaria’: https://www.who.int/malaria/areas/community_case_management/overview/en/
Mother and father, Anette and Noel with their children N’Simba, left and Mbangu right and two healthcare workers.

N’Simba’s story

N’Simba is a bright-eyed toddler growing up with his sister Mbangu and parents Noel and Anette in the village of Katenda, in the south of DRC. The country carries one of the heaviest malaria burdens in the world.

During a follow-up visit at their home by healthcare workers from Katenda’s community health centre, Noel and Anette recall the stressful experience when N’Simba first contracted malaria. Noel remembers clearly the morning he woke up to find N’Simba burning with fever. “N’Simba started to vomit, the fever persisted, and he refused to be breast-fed,” said Noel. They rushed N’Simba to the community health centre by motorbike. Time was precious and N’Simba’s condition seemed to get worse with each passing minute.

On arriving at the community health centre, the nurses quickly tended to N’Simba. After some initial tests, they administered a dose of artesunate rectal capsules and urged Noel and Anette to take N’Simba to the nearest general hospital 50 kilometres away.

With no public transport and a poorly constructed road, the only option for Noel and Anette was to drive N’Simba to hospital by motorbike. On the way, Anette noticed that N’Simba’s fever was starting to drop. Soon after, he even wanted to be fed.

“I stopped my bike in the middle of forestland and Anette was able to breastfeed N’Simba,” said Noel. “We were relieved! This was a good sign already.”

After the long ride, they arrived at the hospital, where the doctor applauded the quick reaction on the part of N’Simba’s parents and the nurses at the health centre. N’Simba was prescribed injectable artesunate and ACT to ensure a complete recovery.

In remote parts of DRC where small villages do not have fully functional hospitals, initiatives like Community Access to Rectal Artesunate for Malaria (CARAMAL) play an important role in helping people access artesunate rectal capsules and therefore buy time to access full treatment for severe malaria.

Anette concluded by saying, “I really appreciate the efficiency with which my son was treated, and I am also impressed by the routine follow-up checks done through the initiative to ensure that N’Simba completely recovered.”

Source: Diaka T Jules/Alain Mugoto, CARAMAL project
Reducing the burden of relapsing malaria

The World Health Organization’s (WHO’s) Global Technical Strategy for Malaria 2016–2030 has set the ambitious target of eliminating malaria from at least 35 countries by 2030. A major challenge in reaching this target is the elimination of Plasmodium vivax, a species of malaria parasite that accounts for half of all cases outside sub-Saharan Africa, and is often predominant in countries that are close to eliminating the disease, such as Thailand and Guatemala. In fact, P. vivax accounts for 70% of malaria cases in countries that have fewer than 5,000 cases per year.

P. vivax causes between 5.9 and 9.3 million clinical infections every year worldwide, many of which are relapses of existing infections that occur in the absence of a new infective mosquito bite. This happens because P. vivax parasites can lie dormant in the liver, reactivating to trigger multiple episodes of malaria, weeks, months or even years after the initial mosquito bite. These relapses not only cause further illness, but also perpetuate the cycle of onward transmission of parasites back into the mosquito during its next blood meal. Until recently, primaquine (PQ) was the only available treatment for preventing relapses of P. vivax malaria. However, ensuring patient compliance of the 7 to 14-day treatment regimen for PQ is difficult, and low compliance can compromise therapeutic efficacy. A reduced-frequency dosing schedule to improve compliance was therefore urgently needed.

In 2018, tafenoquine (TQ; Kozenix/Krintafel), developed in partnership with GlaxoSmithKline (GSK) became the first new treatment for the liver cure (prevention of relapse) of P. vivax malaria in more than 60 years – and the first-ever single-dose treatment for this indication. TQ was approved by both the US Food and Drug Administration and the Australian Therapeutic Goods Administration in 2018, marking a major regulatory milestone for P. vivax elimination efforts. Increasing access to this essential medicine has continued to be a priority for MMV and GSK, with marketing authorization granted in Brazil in 2019 and Thailand in early 2020, and regulatory submissions made in five other P. vivax-endemic countries between 2018 and 2020. MMV and GSK are also seeking to expand access to TQ for one of the most at-risk patient populations (children under 10) through the TEACH7 paediatric study, which will support a regulatory submission anticipated in late 2020.

Both PQ and TQ belong to a class of compounds called the 8-aminoquinolines. In individuals who are deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD), 8-aminoquinolines can destroy red blood cells, potentially causing anaemia. To help identify patients eligible for treatment, GSK’s partner PATH has fostered development of a quantitative point-of-care G6PD diagnostic test, which is now approved in nine P. vivax-endemic countries.

However, despite the relatively low ex-factory cost of TQ, the final in-country cost of the G6PD diagnostic may have an impact on the cost-effectiveness of the complete treatment package – a challenge that MMV, together with PATH, is working to address. Preparations are currently underway to support an implementation study of TQ with the G6PD diagnostic test in Brazil (the TRuST12 study), as well as implementation studies in Thailand and other countries, the results of which are intended to support widespread adoption of these new tools into WHO policy and National Treatment Guidelines.

To support widespread adoption of the new tools to achieve effective radical cure of P. vivax malaria, in April 2019, MMV and PATH announced the ‘VivAccess’ project – a 5-year, jointly-led initiative involving malaria control programmes and other partners in ten countries across Asia, Africa, and Latin America. MMV, PATH and regional groups such as the Asia Pacific Leaders Malaria Alliance are also collaborating to support malaria elimination efforts by developing advocacy strategies and disseminating relevant research and advocacy findings through vivaxmalaria.org. This information hub is available to all countries and is designed to increase global understanding of P. vivax malaria.

In 2019, MMV launched vivaxmalaria.org – a comprehensive repository of information on P. vivax. The website contains key insights, best practices, tools and resources that are suitable for both general and technical audiences. These are shared and uploaded by a consortium of stakeholders involved in the treatment and control of P. vivax malaria. The information hub is currently housed by MMV to support its work with partners on P. vivax malaria. Through vivaxmalaria.org, MMV aims to:

- Increase awareness of relapsing P. vivax malaria
- Inform stakeholders about progress in the development of new tools
- Promote global partnerships to advance the elimination of the disease

2 According to the WHO, 2019, Thailand reported 3,575 cases of P. vivax malaria in 2018 vs. 447 cases of P. falciparum malaria; in the same year, Guatemala reported 3,018 cases of P. vivax vs. 3 cases of P. falciparum.
5 Tafenoquine is marketed as Kozenix in Australia and Krintafel in the USA. Trade marks are owned or licensed to the GSK group of companies.
6 Regulatory submissions have been completed for India, Ethiopia, Colombia, Peru and Vietnam; submissions to Myanmar and the Philippines are underway as of 2020.
7 Tafenoquine Exposure Assessment in Childhood.
8 The current label for TQ restricts its use to patients with at least 70% G6PD activity (however, PQ can be given to people with 30–100% G6PD activity).
9 PATH: an international, non-profit global health organization based in Washington, USA.
10 India, Djibouti, Pakistan, Myanmar, Thailand, Indonesia, Philippines, Cambodia, Saudi Arabia.
11 Compared to the current standard of care in each P. vivax-endemic country.
12 TRuST: Tafenoquine Roll-out Study.
What are the main challenges associated with malaria control in Brazil, particularly given the presence of both *Plasmodium falciparum* and *P. vivax* malaria?

- While there are a number of challenges for malaria control in Brazil, the main concerns are around access to remote populations, logistical issues (e.g. car, boat and fuel) to reach certain areas during the rainy or dry season, and a lack of trained healthcare workers in the field. A major challenge with *P. vivax* malaria is ensuring that people comply with the long treatment regimen (minimum 7 days), as studies show that around 20% of people do not complete treatment. This leads to relapses and continuous onward parasite transmission.

What is the potential impact of TQ on the clinical case management of *P. vivax* in Brazil?

- TQ has similar efficacy to PQ, but it’s a single-dose regimen and so can improve compliance to treatment, which can potentially lead to better control of *P. vivax* malaria and perhaps even elimination in some areas. However, several challenges must first be addressed. Operationalizing quantitative G6PD testing before prescribing TQ for the population will be expensive. Furthermore, we need to ensure quality control of the tests and also train more healthcare workers, so that these can be rolled out across the country. This is why we are conducting an implementation study (TRuST).

How are results from the TRuST study expected to inform policies regarding TQ in Brazil?

- We expect results from the TRuST study to provide insights about the possibilities and associated challenges of TQ implementation in Brazil, particularly regarding its cost-effectiveness (given the additional expense of the G6PD test). The Ministry of Health will analyse the results to define if, when and where it will be possible to use TQ in Brazil.

What is the potential impact of TQ on the clinical case management of *P. vivax* in Brazil?

**Tucked away in a remote corner of the Brazilian Amazon is a village called Nossa Senhora de Fatima. The only way to reach this village is by boat. Located in one of the most endemic regions for relapsing malaria, the inhabitants of this village are very familiar with their local malaria clinic, which provides front-line care. Brazil carries one of the highest burdens of malaria in Latin America, and the Amazon region within the country accounts for 99.5% of all national cases.**

This was the third time in the recent past that Moises Da Silva was seeking treatment for malaria. For a young, able-bodied man like Moises, relapsing malaria is very disruptive. Having now experienced two relapses following his initial infection, Moises can easily recall the specific symptoms. He says, “You feel cold. It’s hot outside, but your body feels cold. You wrap yourself under a pile of sheets, still you shake all over.”

In Amazonian villages like Nossa Senhora de Fatima, the abundant presence of mosquitoes complicates the situation further. There are times when several members of the family are suffering from malaria at the same time. Though not known to be the deadliest killer in the malaria family, *P. vivax* malaria can still kill and has devastating impacts on the social and economic lives of people. People like Moises, who live in remote endemic regions where relapsing malaria is a daily reality, are in need of medicines that can treat *P. vivax* malaria once and for all.

Source: Relapsing malaria in Brazil (film by MMV and ITN Productions)
The Malaria Drug Development Catalyst: accelerating R&D for drug combinations

To minimize the risk of drug resistance when developing antimalarial treatments, two compounds with complementary properties are paired up to form a combination therapy. The rationale behind this is that each compound can protect the other and therefore resistance generation is delayed. With 15 candidate compounds currently in preclinical and clinical development, understanding how these different compounds interact in order to select the best combinations for further development is a complex and critical process.

In 2019, MMV launched the Malaria Drug Development Catalyst – a new legal and scientific platform to promote effective collaboration between industry partners and accelerate the development of next-generation drug combinations. The Catalyst is curated by MMV and contains successful single molecules that have entered translational development. Based on the complementary partner characteristics of the drug candidates, the Catalyst helps to identify the best combinations to take forward for clinical testing and to allow a dialogue and exchange of information between MMV’s partners. This enables faster identification and progression of viable combinations.

The Catalyst is open to MMV’s pharmaceutical partners with drugs in translational development, and currently has four members – Zydus Cadila, Novartis, Merck KGaA and MMV – and of the 30 combinations studied so far, 12 have already demonstrated positive results.

Dr Mukul Jain tells us how the Malaria Drug Development Catalyst is helping to find a combination partner for the promising translational candidate MMV253.

Can you tell us about MMV253’s journey so far?

- MMV253 came out of a discovery partnership between MMV and AstraZeneca in 2014, and was acquired by Zydus in 2016 for non-clinical and clinical development. MMV253 has an exciting profile, rapidly clearing parasites from the blood after a single dose and staying in the blood above the concentration needed to kill parasites for >6 days. The compound has an unknown mechanism of action, is active against both Plasmodium falciparum and Plasmodium vivax, and has shown low resistance potential in in vitro studies. It has also shown a good safety profile in both non-clinical toxicology studies in the lab, as well as in Phase I studies in humans, with no indication currently of potential harm for the developing foetus. This suggests it may be suitable for use during pregnancy.

How is the Malaria Drug Development Catalyst assisting Zydus in the search for a combination partner?

- The Catalyst is a great initiative and we are very excited to be a part of it. Given the promising efficacy and safety data we have gathered from studies conducted so far in healthy volunteers, now is the right time to identify a partner for MMV253 and map out a clinical development strategy. By bringing together industry partners of different sizes and backgrounds, and with candidates at similar stages of development, the Catalyst is helping us identify compatible partners for MMV253. Such collaboration is not always common among the private healthcare sector, so this is a really innovative model.

What has it been like working with MMV?

- No other organization in the world has the same depth of knowledge and expertise in malaria drug development as MMV. At Zydus, being able to tap into MMV’s expertise is a great benefit to us and will hopefully ensure that MMV253 can one day become a treatment option for malaria. Zydus recognizes the need to bring forward new and affordable therapies for malaria, especially for use in highly endemic countries such as India, which currently carries the world’s highest burden of P. vivax malaria.1

1 According to the WHO World Malaria Report 2019, 47% of the global P. vivax burden is in India: https://www.who.int/publications-detail/world-malaria-report-2019
Discovering new candidate antimalarial drugs

The discovery of new antimalarial drugs is a lengthy and costly process, typically taking 12 to 15 years from early discovery activities to the point when the drug is available to patients. MMV’s Discovery team is small, but through collaboration with centres of excellence around the world, huge progress has been made in delivering high-quality antimalarial candidates. To date, over seven million compounds have been screened against \textit{P. falciparum} – representing one of the single largest screening campaigns against a pathogenic organism in history, and resulting in the delivery of 24 new candidate drugs.\(^2\)

Finding out how these compounds work is important, as they can often lead to new molecular targets and mechanisms. MMV is a founding member of the MaLaria Drug Accelerator (MaLDA) – a network of 13 academic and industry partners funded by the Bill & Melinda Gates Foundation, which is focused on unravelling the mechanisms by which these confirmed antimalarial compounds work, and on delivering lead series acting through such mechanisms into the global portfolio.

Countering the ongoing threat of resistance

MMV’s treasure trove of new candidates eligible for clinical development is a key resource for developing new medicines that would be useful if there were widespread failure of the current artemisinin-based combination therapies (ACTs). However, it is important to maximize the chances that these new molecules are not themselves prone to rapid selection of resistance. In 2019, MMV set up a new ‘resistance workflow’, whereby all new candidate molecules moving forward are routinely profiled for their robustness against resistance in standardized assays. The purpose of this is to allow MMV and its partners to prioritize compounds with a low propensity to select for resistance. MMV’s discovery portfolio currently contains 33 distinct chemical series, 21 with a known mechanism of action, and 12 for which the mechanism is unknown. These latter 12 are particularly interesting, as they are fast killing and not cross resistant; three compounds have been unable to identify resistant mutants when the compounds are incubated with a billion parasites for 60 days in the laboratory (e.g. see pp. 36–37) and the same studies are planned to explore the ‘irresistibility’ of the other nine. It’s important to note, however, that historically, compounds such as artesunate, lumefantrine and pyronaridine also successfully cleared this hurdle.

In 2019, three new compounds entered MMV’s portfolio as preclinical candidates, each with its own unique and interesting profile.

\section*{MMV183}

MMV183 (TropIQ) is the first Dutch antimalarial preclinical candidate, arising from a Netherlands-based discovery consortium set up in 2016 by MMV and Lygature (a Dutch public–private life sciences partnership), and funded by the Dutch government. MMV183 is an anti-metabolite, fast-killing compound with potent transmission-blocking activity and a low predicted oral dose in adults. Preclinical studies are currently underway.

\section*{MMV646}

MMV646 (JPC-3210) is a highly potent compound active against both \textit{P. falciparum} and \textit{P. vivax}. It has demonstrated very low resistance potential \textit{in vitro} and exhibited curative activity after a single dose in SCID models.\(^3\) In 2019, an agreement was signed with Jacobus Pharmaceuticals for further development of MMV646, and preclinical dose-range-finding studies were initiated in December of that year.

\section*{INE963}

INE963, developed in collaboration with Novartis and awarded MMV’s Project of the Year 2019 (pp. 36–37), has an unknown, irresistible mechanism of action, and has demonstrated an ability to rapidly clear parasites from the blood. The compound will now undergo GLP safety studies and will be assessed as a potential combination partner.
Developing new approaches to malaria prophylaxis

As countries move towards elimination of malaria, natural immunity to the parasite will decline and there will be an increasing need for new prophylaxis strategies to ensure populations remain malaria free. Furthermore, there is a critical need to protect vulnerable populations such as children in areas of high seasonal malaria transmission (pp. 21–22).

In an effort to develop new strategies for prophylaxis, MMV is exploring the potential of long-acting injectable formulations. P218, currently in Phase I development, is one such compound currently being explored (in collaboration with Janssen) as a potential long-acting, single-administration, injectable prodrug for prophylaxis. P218 inhibits a well-defined, clinically validated enzyme target, dihydrofolate reductase, and is active against both the blood stage and liver stage of the parasite life cycle.

After a mosquito bite, malaria parasites first enter the liver, where they multiply before entering the blood. Killing the parasite at the liver stage of development can therefore prevent a malaria infection from taking hold, effectively blocking disease progression and preventing the emergence of symptoms. In 2019, P218 demonstrated promising activity in the sporozoite VIS model,4 designed specifically to assess liver-stage prophylactic activity, in Antwerp, Belgium (further studies are ongoing).

In addition, two prodrugs5 of atovaquone (MMV370 and MMV371), produced by Calibr,6 USA, underwent preclinical studies in 2019. Both prodrugs have shown high liver-stage activity in laboratory models, remaining in the blood for a long time after a low-dose injection, and will now undergo further formulation and good laboratory practice safety studies.

MMV at the cutting edge of artificial intelligence: machine learning

MMV recognizes the power of machine learning and Big Data in providing quicker, cheaper and more effective drug discovery solutions. By leveraging artificial intelligence to identify patterns from data sets, MMV has developed an in silico model7 – the first ever in antimalarial drug discovery – to predict which compounds have potential blood-stage activity against malaria. This model will help to identify which compounds to screen, thus expediting the discovery of blood-stage inhibitors. The tool will soon be made publicly available on ChEMBL, a manually curated chemical database of bioactive molecules with drug-like properties.8 In addition, MMV has initiated a collaboration with AstraZeneca to explore the impact of machine learning on medicinal chemistry within a drug discovery project.
Optimizing data management to streamline antimalarial research

MMV’s Discovery team is routinely working on more than 25 research projects, supported by 25 technology platforms. These platforms, which are located all over the world, test very large numbers of compounds to evaluate their activity against different stages of the parasite life cycle. Central to the success of this large-scale research effort is a streamlined system of storing, tracking and dispatching compounds to MMV’s partners, which enables rapid delivery of compounds throughout the world to accelerate drug discovery initiatives. The workflow also generates large volumes of data that must be deposited in a standardized format, stored securely and easily accessed by the relevant teams.

Dominique Besson tells us more about the processes that MMV has put in place to manage the huge quantities of data generated by its partners.

Please tell us about your work as Associate Director, Discovery Data at MMV.

In the context of a virtual R&D organization like MMV, it is important to ensure homogeneity in the way that data is collected, analyzed and reported. In my role, I have two main responsibilities. Firstly, as a compound manager, I ensure that molecules for testing are available at the right time and are of the right quality. Secondly, as a data manager, I check that the data generated by MMV’s various research partners are comparable, by making sure, for example, that all results are reported in the same standardized units.

Day to day, I have certain ‘preventive’ duties, such as formulating rules, processes and guidelines relating to the database, as well as providing appropriate training to both internal and external end-users. In addition, I have ‘corrective’ duties, such as taking actions to correct processes or workflows whenever MMV’s quality control guidelines are not followed properly.

What is the importance of databases in research?

Data are the currency of drug discovery, and MMV’s database is the bank where we save these data. The importance of MMV’s database is that it stores, as well as connects, all chemical and biological information in a single place. When information is well connected, it is possible for a scientist to better understand how modifying the structure of a particular chemical compound is likely to impact its biological activity.

The information kept in a database effectively forms a kind of ‘roadmap’, which explains how and why a particular project reached a particular decision point. It is critical for this information to be easily extractable — and in a format that is useful for specific users. For example, we have developed a specific method of extracting preclinical data from the database, in a format that helps the translational team to predict the human dose of a particular compound. Insights like these are invaluable to the progress of the portfolio.

What tools does MMV use to manage its data?

MMV’s data repository is called ScienceCloud, which, as its name suggests, is a cloud-based solution developed commercially that stores all data generated by MMV’s research partners. A second tool, the Logistics Management Tool, was developed in-house to help manage compound logistics. Developed initially for tracking compounds internally, the tool will be further modified to grant access to external users to facilitate communication. Both databases are integrated with one another to provide MMV’s discovery and translational teams with up-to-date information on particular compounds or assays.

How do you guarantee the quality of the data you receive?

MMV’s Discovery team ensures the quality of the data it collects and stores in its database by applying basic rules – defined by the acronym QUARTZ. This internal checklist allows us to confirm that data are:

1) of the expected Quality
2) Useful to the projects
3) Accessible to the end-user
4) Relevant for decision-making
5) Traceable to their origin
6) standardized according to MMV’s guidelines.

If data adhere to these six principles, we can be confident that the data are of an acceptable quality.
In the modern era of increased air travel and densely concentrated, interconnected populations, the world is more vulnerable to pandemic diseases than ever before, as seen by the recent and ongoing outbreaks of COVID-19, Ebola, Zika, chikungunya, dengue fever, Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS) and influenza. Now more than ever, new and innovative approaches are urgently needed to mobilize the potential for discovering new drugs to fight global health emergencies.

Under its ethos of ‘openness’, MMV has pioneered several drug discovery initiatives to support R&D efforts in malaria and other neglected tropical diseases. Open-access libraries, such as the Malaria Box, Pathogen Box, Stasis Box, Pandemic Response Box and larger compound collections have catalysed drug discovery research across the globe. These libraries contain drug-like compounds that researchers can use to screen against neglected or pandemic diseases. So far, around 700 of these open-access libraries have been distributed worldwide free of charge, and findings from them have led to over 110 publications, adding significantly to the global scientific knowledge base.

Prof. Lyn-Marie Birkholtz tells us more about her research experience with the Pandemic Response Box.

What made you want to request the Pandemic Response Box?

- The Pandemic Response Box is a really exciting tool for a researcher, as it contains compounds with antiviral, antibacterial and antifungal properties. This allows us to identify entirely new targets that we might not otherwise identify from screening only antimalarial compound libraries, with the aim of repurposing these new targets against malaria.

Have you had any success in identifying hits so far?

- We have identified a number of hits. Some of them target all stages of the parasite life cycle (we call these ‘pan-reactive hits’), while others appear to target one or more specific stages. We are particularly excited about the stage-specific hits as we have found activity against both the asexual and sexual (gametocyte) blood stages of the life cycle. Targeting gametocytes, the reproductive form of the malaria parasite, would allow us to prevent transmission of parasites back into the mosquito during its next blood meal, effectively breaking the parasite’s life cycle and preventing another cycle of reinfection.

How are you collaborating with the MaLaria Drug Accelerator (MaLDA)?

- As part of our testing, we are trying to profile the mechanisms of action of the hits we have identified from the Pandemic Response Box. Some of these compounds already have very well characterized mechanisms of action in other diseases, which certainly helps to focus our research, but other compounds don’t. MaLDA, a network of academic and industry partners, gives us access to drug discovery techniques and resistance screening tools that enable us to profile these compounds much quicker.

In the wider context of malaria eradication, how important is drug discovery in terms of identifying and bringing forward next-generation antimalarial compounds?

- We have learnt from the past that we cannot rely on a single approach to achieve eradication. Continued efforts are needed to develop next-generation drugs that not only treat symptomatic patients but can also eliminate the parasite reservoir of asymptomatic patients. We must remain innovative and explore new chemical and biological targets, as well as develop tools to assess and predict the efficacy of compounds as early as possible in the development process.

What has it been like working with MMV?

- It has been extraordinary. With MMV’s support, we have been able to accelerate the progress of our discovery initiatives. In South Africa, we have a proud record in antimalarial drug discovery, having brought forward MMV048 with another of MMV’s partners, Prof. Kelly Chibale at the University of Cape Town. It is collaborations like these that have allowed us to come so far, so quickly, in antimalarial drug discovery.
Enriching the drug discovery pipeline with an ‘irresistible’ compound

MMV Project of the Year 2019: discovery of novel compound, INE963

MMV’s Project of the Year 2019 is awarded to a discovery team led by Dr Thierry Diagana at the Novartis Institute for Tropical Diseases (NITD) and Dr Brice Campo, Senior Director, Drug Discovery at MMV, for delivering a promising new and ‘irresistible’ preclinical candidate, INE963. The compound is ‘irresistible’ in the sense that it has not been possible to generate resistance to it in the laboratory.

Decreased activity of artemisinine and new resistance to partner drugs in artemisinin-based combination therapies (ACTs), such as piperazine, has led to treatment failures with some ACTs in South East Asia. New medicines with novel mechanisms of action are thus urgently needed. These should have a low propensity to select for resistance, otherwise their lifespan once deployed in the field will be limited. Experience with ACTs shows that the last day of a 3-day course is often not taken, and this brings two risks. First, the obvious risk is to the patient, who does not receive a full course of treatment, but the second hidden risk is to the drug, since this behaviour increases the probability of resistant parasites developing.

MMV has had a collaboration with Novartis over the last 15 years through the NITD, which recently relocated from Singapore to San Francisco. INE963, approved as a preclinical candidate by MMV’s ESAC in 2019 is now the third clinical candidate that has come from the NITD group. It is a very exciting molecule with a number of extremely desirable properties that could make it a potent weapon for combatting resistance as part of a next-generation, reduced-dose combination therapy.

2 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.

The compound is ‘irresistible’ in the sense that it has not been possible to generate resistance to it in the laboratory.
Can you tell us about the discovery of INE963?

**TD** INE963 was discovered through phenotypic screening, in which we screened 1.5 million compounds against the parasite within human red blood cells, without making any prior assumptions about the molecular target. We then filtered the compounds that met these criteria, known as ‘hits’, to select compounds that were not only effective in clearing parasites from the blood, but also had a rapid onset of action. Several new molecular scaffolds emerged from the screening, and after considerable optimization of one of these scaffolds using medicinal chemistry, we ultimately arrived at INE963 as the candidate of choice.

What are the attributes of INE963 that make it a promising antimalarial candidate?

**TD** INE963 rapidly kills and clears parasites and stays in the blood for a long time – key characteristics necessary for a potential single-dose cure. The compound does not significantly inhibit cytochrome P450s, meaning that the risk of a drug-drug interaction between INE963 and a partner drug in a future combination therapy is currently low. INE963 also has good oral bioavailability and physical and chemical properties, important considerations that minimize dose size, cost and formulation risks associated with developing a new medicine suitable for use in young children.

**BC** Importantly, when tested against resistant parasites engineered in the laboratory, as well as known resistant parasites isolated from different malaria-endemic regions of the world, the compound maintains its efficacy. In addition, we have not been able to generate de novo resistance in vitro in the laboratory to date. Although this does not mean that resistance will never be forthcoming, this is very exciting, since a new compound with a novel mechanism of action and a low propensity to select for resistance has great potential. The next steps for INE963 will be to complete manufacturing, toxicology and GLP-compliant safety studies before progressing to Phase I trials in humans.

How has team collaboration contributed to the success of the project?

**TD** The collaboration between Novartis and MMV started back in 2006, with partners, but this project with NITD was initiated in 2017/2018 following a physical move from Singapore to California, USA. Thanks to the commitment of some critical members of the Singapore leadership team, we rebuilt the team and our infrastructure almost from scratch in Emeryville. Under the leadership of Chris Sarko, Director of Medicinal Chemistry, we are proud that focused collaboration and rapid optimization of the compound series delivered such a high-quality candidate in 2019.

For a disease like malaria with a high global burden and the threat of emerging resistance, we need to stay on top of all new innovations and harvest the fruit of new approaches. By connecting collaborators through its extensive network, MMV captures the breadth of innovation happening in the malaria landscape and helps to inform new drug discovery approaches that we can adopt to develop next-generation medicines; for example, we have been fortunate to benefit from the direct input of Sir Simon Campbell as a mentor from ESAC. MMV’s knowledge and experience in malaria, combined with our expertise in drug development, has created a strong and productive partnership.

**BC** MMV has a long history of collaboration with Novartis and the relationship is extremely strong. Previous front runner compounds from the same chemical series as INE963 have not progressed because of in vitro and preclinical toxicity findings. However, the team applied what we have learnt from these experiences to identify a new and better-tolerated compound to move forward to preclinical testing. As Thierry mentioned above, after the start of this project, NITD moved its operational base from Singapore to California, which could easily have slowed, or even halted, progress. However, the new team was established and worked hard to maintain a high level of collaboration and productivity during this transition period, keeping the project on track. The momentum thus achieved was truly impressive.

How does it feel to receive MMV’s Project of the Year award?

**TD** To be recognized as MMV’s Project of the Year gives us a great sense of pride, and reflects the exciting potential of this new molecule. It is particularly satisfying to receive the award on the 10th anniversary of Novartis’s collaboration with MMV, which began with the discovery of cipargamin back in 2009, for which we received the 2009 MMV Project of the Year!

**BC** As the MMV project director, I’ve been part of this team for the past 8 years now. We are a young and passionate team, and I’m delighted that we have been able to deliver a high-quality compound. Going forward, MMV and Novartis will continue to learn from each other, and we hope that many more molecules will come out of this collaboration in the future.
2019 was a successful year for MMV.

Total revenues amounted to 93.4 million United States dollars (USD) (2018: USD 97.2 million), largely thanks to the continued commitment of our donors (in total USD 71.4 million) and partly owing to the indemnity payment of EUR 17 million (equivalent to USD 19.4 million) executed by our pharmaceutical partner Sanofi. This payment was to support the completion, under MMV's operational responsibility and leadership as of 1 January 2019 of the Phase II artefenomel/ferroquine drug combination development programme. This amount was booked in 2018 as "deferred revenue".

Total expenditure in 2019 reached a level of USD 96.6 million. This represented a 14% increase relative to the previous year (USD 84.5 million in 2018). Research & development (R&D) investments amounted to USD 66.0 million (up 18% compared to USD 55.6 million in 2018), including significant investments in the above-mentioned Phase II artefenomel/ferroquine development programme. Access & product management (APM) expenditure increased to USD 15.3 million (up 11% compared to USD 13.7 million in 2018). In 2019, corporate affairs, administration & finance, and board meetings expenditure (portfolio support expenditure) cumulatively accounted for 12.7% of total expenditure and 14.5% of R&D and APM (portfolio) expenditure, in line with previous years.

In 2019, the Bill & Melinda Gates Foundation (BMGF) paid to MMV the first USD 14 million of the new USD 180 million 5-year core grant for the period 1 July 2019 – 30 June 2024, the largest single donation ever pledged to MMV since its foundation in 1999. In 2019, MMV received new grants from the European and Developing Countries Clinical Trials Partnership (EDCTP), the Australian Government Department of Foreign Affairs and Trade (DFAT), the Program for Appropriate Technology in Health (PATH), the Swiss Agency for Development and Cooperation (DEZA/SDC), the Global Health Innovative Technology Fund (GHIT), the Research Investment for Global Health Technology Fund (RIGHT Fund), as well as additional funding to the current 2017–2021 core grant from the UK Department for International Development (DFID). MMV is grateful for these and previous commitments from its donors.

Following an EUR 8.7 million (equivalent to USD 9.8 million) pre-payment from the European and Developing Countries Clinical Trials Partnership (EDCTP), which was executed in late December 2019, to support 2020 and 2021 grant activities, MMV's total cash balance as of 31 December 2019 amounted to USD 57.2 million (2018: USD 57.4 million). Total unrestricted funds increased to USD 59.4 million (2018: USD 51.9 million), of which USD 4.0 million was paid-in capital,
New pledges received in 2019

<table>
<thead>
<tr>
<th>Donor</th>
<th>Amount in USD</th>
<th>Amount in original currency</th>
<th>Grant</th>
<th>Time period</th>
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<tr>
<td>European and Developing Countries Clinical Trials Partnership (EDCTP)</td>
<td>24 434 376</td>
<td>EUR 21 990 938</td>
<td>PAMAFRICA</td>
<td>2020–2024</td>
</tr>
<tr>
<td>UK Department for International Development (DFID)</td>
<td>13 071 895</td>
<td>GBP 10 000 000</td>
<td>Additional funding to 2017–2021 grant</td>
<td>Apr 2019 – Mar 2021</td>
</tr>
<tr>
<td>PATH</td>
<td>3 966 074</td>
<td>USD 3 966 074</td>
<td>VvAccess supply grant</td>
<td>2019–2023</td>
</tr>
<tr>
<td>Swiss Agency for Development and Cooperation (DEZA/SDC)</td>
<td>1 855 670</td>
<td>CHF 1 800 000</td>
<td>Antimalarial treatment options for pregnant women</td>
<td>Oct 2019 – Dec 2021</td>
</tr>
<tr>
<td>GHIT</td>
<td>484 404</td>
<td>JPY 52 800 000</td>
<td>H2018-101: new hit-to-lead activity between MMV and Takeda</td>
<td>2018-2019</td>
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<tr>
<td>Research Investment for GHIT Fund (RIGHT Fund)</td>
<td>582 399</td>
<td>KRW 675 000 000</td>
<td>Continuous process development and scale-up for ozonolysis</td>
<td>June 2019 – Mar 2022</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>46 158 557</strong></td>
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</table>
Financial management
The philosophy underlying MMV’s financial management is that of prudent, conservative control, including appropriate return on interim treasury investments. Forecasting various long-term funding and income scenarios enables MMV to manage its growing R&D portfolio more effectively. It also provides a baseline analysis for fundraising activities aimed at financing the portfolio in line with long-term projections. Given the unsteady financial environment and market conditions, it is evident that the portfolio, cash flow and new potential fundraising opportunities must be managed dynamically and seamlessly. As an ethical healthcare organization, MMV maintains sufficient funds to support the completion of ongoing clinical studies, related publication of clinical data, reporting and regulatory obligations, including those outlined by the ICH.

Banking relationships
Cash and cash equivalents represent the largest portion of MMV’s total assets. Relationships with four major Swiss banks allow MMV to effectively manage cash resources and diversify risk. The banks provide services such as current accounts, and investment and cash management facilities, in multiple currencies. The aforementioned Foundation Fund is managed by an investment manager, which is part of a major US investment banking group, under the terms of a discretionary portfolio management mandate and under the supervision of the Board of Directors of MMV.

Foreign exchange exposure
MMV operates in a multi-currency environment. Cash inflows from donors are largely received in US dollars (USD) and UK pounds sterling (GBP), and a smaller portion in other currencies, such as Swiss francs (CHF), euros (EUR), Australian dollars (AUD) and Japanese yen (JPY). Cash outflows for R&D and APM projects are mostly in USD, which is the standard currency used in the various contractual agreements signed with each project partner and therefore a natural cover for financial exchange risk. Being a Swiss-based organization, many operational expenses are in CHF. Throughout the financial year, MMV’s management strives to maintain a natural hedged position, whereby the breakdown of cash available by currency mirrors the estimated breakdown of expenditure by currency. The reference currency for accounting at MMV is USD.

Financial reporting standards
The consolidated financial statements (including MMV North America Inc.) are prepared in compliance with the Swiss Generally Accepted Accounting Principles (Swiss GAAP FER), as well as the requirements of the Swiss Code of Obligations. The organization’s operating procedures are constantly updated in line with evolving requirements. MMV also issues stand-alone financial statements, which are prepared in compliance with the Swiss Code of Obligations (articles 957 to 963b, in force since 1 January 2013).

Foundation capital
By 31 December 2003, the stipulated foundation capital of USD 4 million was fully subscribed (in a Swiss foundation it is a legal requirement that foundation capital be constituted without delay, to provide a degree of financial security). The foundation capital has since remained unchanged.

Financial tables
The following financial tables and notes are extracted from the Swiss GAAP FER-compliant accounts.

Figure 5: MMV income and expenditure to date and scenario 2020–2024

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Medicines for Malaria Venture  |  Annual report 2019
Report on extracted elements of consolidated financial statements to the management of

MMV MEDECINES FOR MALARIA VENTURE, Meyrin

We have audited the consolidated financial statements of the MMV MEDECINES FOR MALARIA VENTURE for the year ended 31 December 2019 from which the extracted elements of consolidated financial statements were derived, in accordance with Swiss law and Swiss Auditing Standards. In our report dated 25 March 2020, we expressed an unqualified opinion on the consolidated financial statements from which the extracted elements of consolidated financial statements were derived.

In our opinion, the accompanying extracted elements of consolidated financial statements are consistent, in all material respects, with the consolidated financial statements from which they were derived.

For a better understanding of the organisation’s financial position and the results of its operations for the period and of the scope of our audit, the extracted elements of consolidated financial statements should be read in conjunction with the consolidated financial statements from which the extracted elements of consolidated financial statements were derived and our audit report thereon.

KPMG SA

Hélène Bèrquin
Licensed Audit Expert
Auditor in Charge

Jérôme Gauss
Licensed Audit Expert

Geneva, 25 March 2020

Enclosure:
- Extracted elements of the consolidated financial statements (page 43 to 51 included)
### MMV CONSOLIDATED STATEMENT OF FINANCIAL POSITION

#### ASSETS

<table>
<thead>
<tr>
<th>Notes</th>
<th>31 Dec 2019 USD</th>
<th>31 Dec 2018 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash and cash equivalents</td>
<td>57,233,655</td>
<td>57,409,733</td>
</tr>
<tr>
<td>Donations receivable</td>
<td>426,174</td>
<td>7,692,689</td>
</tr>
<tr>
<td>Accounts receivable</td>
<td>788,720</td>
<td>17,231,665</td>
</tr>
<tr>
<td>Tax receivable</td>
<td>263,992</td>
<td>47,950</td>
</tr>
<tr>
<td>Prepaids</td>
<td>735,240</td>
<td>645,574</td>
</tr>
<tr>
<td>Prepaid portfolio commitments</td>
<td>907,157</td>
<td>951,408</td>
</tr>
<tr>
<td><strong>Total current assets</strong></td>
<td><strong>60,354,938</strong></td>
<td><strong>83,979,019</strong></td>
</tr>
<tr>
<td>Long-term assets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term receivables</td>
<td>15,567,566</td>
<td>14,213,484</td>
</tr>
<tr>
<td>Investment portfolio - Foundation Fund</td>
<td>14,431,325</td>
<td>-</td>
</tr>
<tr>
<td>Guarantees</td>
<td>234,087</td>
<td>215,103</td>
</tr>
<tr>
<td>Fixed assets, net</td>
<td>256,722</td>
<td>175,554</td>
</tr>
<tr>
<td><strong>Total long-term assets</strong></td>
<td><strong>30,489,700</strong></td>
<td><strong>14,604,141</strong></td>
</tr>
<tr>
<td><strong>TOTAL ASSETS</strong></td>
<td><strong>90,844,638</strong></td>
<td><strong>98,583,160</strong></td>
</tr>
</tbody>
</table>

#### LIABILITIES, CAPITAL & RESERVES

##### Current liabilities

<table>
<thead>
<tr>
<th></th>
<th>31 Dec 2018 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accrued portfolio commitments</td>
<td>15,103,931</td>
</tr>
<tr>
<td>Deferred revenue</td>
<td>9,793,333</td>
</tr>
<tr>
<td>Other creditors</td>
<td>1,502,697</td>
</tr>
<tr>
<td>Accrued expenses</td>
<td>2,748,345</td>
</tr>
<tr>
<td>Short-term provisions</td>
<td>836,540</td>
</tr>
<tr>
<td><strong>Total current liabilities</strong></td>
<td><strong>29,986,846</strong></td>
</tr>
</tbody>
</table>

##### Restricted operating funds

<table>
<thead>
<tr>
<th></th>
<th>31 Dec 2018 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total restricted funds</strong></td>
<td><strong>1,506,750</strong></td>
</tr>
</tbody>
</table>

##### Unrestricted funds

<table>
<thead>
<tr>
<th></th>
<th>31 Dec 2018 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paid-in capital</td>
<td>4,000,000</td>
</tr>
<tr>
<td>Foundation Fund</td>
<td>29,998,911</td>
</tr>
<tr>
<td>Unrestricted operating funds</td>
<td>25,352,131</td>
</tr>
<tr>
<td><strong>Total restricted funds</strong></td>
<td><strong>59,351,042</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>31 Dec 2019 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL LIABILITIES, CAPITAL &amp; RESERVES</strong></td>
<td><strong>90,844,638</strong></td>
</tr>
</tbody>
</table>

### MMV CONSOLIDATED STATEMENT OF CHANGES IN CAPITAL

<table>
<thead>
<tr>
<th></th>
<th>Balance at 1 January 2018</th>
<th>Internal funds transfer</th>
<th>Gain/(loss) for the period</th>
<th>Balance at 31 December 2018</th>
<th>Internal funds transfer</th>
<th>Gain/(loss) for the period</th>
<th>Balance at 31 December 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restricted operating funds</td>
<td>17,202,032</td>
<td>(938,565)</td>
<td>(4,997,758)</td>
<td>11,265,709</td>
<td>(7,296,894)</td>
<td>(2,462,065)</td>
<td>1,506,750</td>
</tr>
<tr>
<td><strong>TOTAL RESTRICTED OPERATIONS FUNDS</strong></td>
<td><strong>17,202,032</strong></td>
<td><strong>(938,565)</strong></td>
<td><strong>(4,997,758)</strong></td>
<td><strong>11,265,709</strong></td>
<td><strong>(7,296,894)</strong></td>
<td><strong>(2,462,065)</strong></td>
<td><strong>1,506,750</strong></td>
</tr>
<tr>
<td>Paid-in capital</td>
<td>4,000,000</td>
<td>-</td>
<td>-</td>
<td>4,000,000</td>
<td>-</td>
<td>-</td>
<td>4,000,000</td>
</tr>
<tr>
<td>Foundation Fund</td>
<td>-</td>
<td>-</td>
<td>28,426,969</td>
<td>28,426,969</td>
<td>-</td>
<td>1,571,942</td>
<td>29,998,911</td>
</tr>
<tr>
<td>Unrestricted operating funds</td>
<td>29,827,127</td>
<td>938,565</td>
<td>(11,260,084)</td>
<td>19,505,608</td>
<td>7,296,894</td>
<td>(1,450,371)</td>
<td>25,352,131</td>
</tr>
<tr>
<td><strong>TOTAL UNRESTRICTED FUNDS</strong></td>
<td><strong>33,827,127</strong></td>
<td><strong>938,565</strong></td>
<td><strong>(17,166,885)</strong></td>
<td><strong>51,932,577</strong></td>
<td><strong>7,296,894</strong></td>
<td><strong>121,571</strong></td>
<td><strong>59,351,042</strong></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>51,029,159</strong></td>
<td>-</td>
<td><strong>12,169,127</strong></td>
<td><strong>63,198,286</strong></td>
<td>-</td>
<td><strong>(2,340,494)</strong></td>
<td><strong>60,857,792</strong></td>
</tr>
</tbody>
</table>
## MMV CONSOLIDATED STATEMENT OF OPERATIONS FOR THE PERIOD ENDED

### REVENUE

<table>
<thead>
<tr>
<th>Description</th>
<th>31 Dec 2019 USD</th>
<th>31 Dec 2018 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donation revenue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restricted donation</td>
<td>12 566 312</td>
<td>16 706 770</td>
</tr>
<tr>
<td>Unrestricted donation</td>
<td>58 825 439</td>
<td>48 172 607</td>
</tr>
<tr>
<td><strong>Total donation revenue</strong></td>
<td><strong>7 71 391 751</strong></td>
<td><strong>64 879 377</strong></td>
</tr>
<tr>
<td>Restricted revenue from partnerships</td>
<td>19 351 128</td>
<td>2 779 818</td>
</tr>
<tr>
<td>Unrestricted revenue from partnerships</td>
<td>2 562 760</td>
<td>29 404 655</td>
</tr>
<tr>
<td>Other unrestricted revenue</td>
<td>118 474</td>
<td>154 547</td>
</tr>
<tr>
<td><strong>Total other revenue</strong></td>
<td><strong>22 032 362</strong></td>
<td><strong>32 339 020</strong></td>
</tr>
<tr>
<td><strong>TOTAL REVENUE</strong></td>
<td><strong>93 424 113</strong></td>
<td><strong>97 218 397</strong></td>
</tr>
</tbody>
</table>

### EXPENDITURE

<table>
<thead>
<tr>
<th>Description</th>
<th>31 Dec 2019 USD</th>
<th>31 Dec 2018 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portfolio expenditure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discovery project expenditure</td>
<td>22 266 240</td>
<td>26 627 649</td>
</tr>
<tr>
<td>Translational project expenditure</td>
<td>20 122 690</td>
<td>16 719 151</td>
</tr>
<tr>
<td>Development project expenditure</td>
<td>23 622 642</td>
<td>12 285 924</td>
</tr>
<tr>
<td>Access &amp; product management project expenditure</td>
<td>15 271 157</td>
<td>13 698 153</td>
</tr>
<tr>
<td>Other portfolio expenditure</td>
<td>3 021 284</td>
<td>2 899 091</td>
</tr>
<tr>
<td><strong>Total portfolio expenditure</strong></td>
<td><strong>84 304 013</strong></td>
<td><strong>72 229 968</strong></td>
</tr>
<tr>
<td>Support of portfolio expenditure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Board meetings expenditure</td>
<td>329 817</td>
<td>349 639</td>
</tr>
<tr>
<td>Corporate affairs expenditure</td>
<td>5 834 979</td>
<td>4 900 568</td>
</tr>
<tr>
<td>Administration &amp; finance expenditure</td>
<td>6 084 948</td>
<td>6 184 330</td>
</tr>
<tr>
<td><strong>Total support of portfolio expenditure</strong></td>
<td><strong>12 249 744</strong></td>
<td><strong>11 434 537</strong></td>
</tr>
<tr>
<td>Funding reimbursements</td>
<td>36 640</td>
<td>833 097</td>
</tr>
<tr>
<td><strong>Other expenses</strong></td>
<td><strong>36 640</strong></td>
<td><strong>833 097</strong></td>
</tr>
<tr>
<td><strong>TOTAL EXPENDITURE</strong></td>
<td><strong>96 590 397</strong></td>
<td><strong>84 497 602</strong></td>
</tr>
<tr>
<td><strong>RESULT FROM OPERATING ACTIVITIES</strong></td>
<td><strong>(3 166 284)</strong></td>
<td><strong>12 720 795</strong></td>
</tr>
<tr>
<td>Financial Income</td>
<td>1 005 032</td>
<td>270 782</td>
</tr>
<tr>
<td>Financial Expenses</td>
<td>(179 243)</td>
<td>(822 450)</td>
</tr>
<tr>
<td><strong>Net financial result</strong></td>
<td><strong>825 789</strong></td>
<td><strong>(551 668)</strong></td>
</tr>
<tr>
<td>Of which are related to the Foundation Fund</td>
<td>217 861</td>
<td>-</td>
</tr>
<tr>
<td><strong>NET SURPLUS PRIOR TO ALLOCATIONS</strong></td>
<td><strong>(2 340 495)</strong></td>
<td><strong>12 169 127</strong></td>
</tr>
<tr>
<td><strong>ALLOCATIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfer (to) from unrestricted operating funds</td>
<td>1 450 371</td>
<td>11 260 084</td>
</tr>
<tr>
<td>Transfer (to) from Foundation Fund</td>
<td>(1 571 942)</td>
<td>(28 426 969)</td>
</tr>
<tr>
<td>Transfer (to) from donor restricted operating funds</td>
<td>2 462 066</td>
<td>4 997 758</td>
</tr>
<tr>
<td><strong>NET SURPLUS AFTER ALLOCATIONS</strong></td>
<td><strong>-</strong></td>
<td><strong>-</strong></td>
</tr>
</tbody>
</table>
MMV CONSOLIDATED STATEMENT OF CASH FLOW FOR THE PERIOD ENDED

<table>
<thead>
<tr>
<th>Notes</th>
<th>2019</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>(LOSS)/SURPLUS FOR THE YEAR</td>
<td>(2,340,495)</td>
<td>12,169,127</td>
</tr>
<tr>
<td>CASH FLOW FROM OPERATING ACTIVITIES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in provisions</td>
<td>6</td>
<td>69,571</td>
</tr>
<tr>
<td>Depreciation</td>
<td>4</td>
<td>96,414</td>
</tr>
<tr>
<td>(Increase)/decrease in donations receivable</td>
<td></td>
<td>7,375,147</td>
</tr>
<tr>
<td>(Increase)/decrease in accounts receivable</td>
<td>8</td>
<td>16,442,945</td>
</tr>
<tr>
<td>(Increase)/decrease in tax receivable</td>
<td></td>
<td>(216,042)</td>
</tr>
<tr>
<td>(Increase)/decrease in portfolio-related prepaid expenses</td>
<td></td>
<td>44,251</td>
</tr>
<tr>
<td>(Increase)/decrease in prepaid expenses</td>
<td></td>
<td>(89,666)</td>
</tr>
<tr>
<td>Increase/(decrease) in accrued portfolio-related commitments</td>
<td></td>
<td>2,983,289</td>
</tr>
<tr>
<td>Increase/(decrease) in deferred revenue</td>
<td>9</td>
<td>(9,677,216)</td>
</tr>
<tr>
<td>Increase/(decrease) in other creditors</td>
<td></td>
<td>487,763</td>
</tr>
<tr>
<td>Increase/(decrease) in accrued expenses</td>
<td></td>
<td>573,712</td>
</tr>
<tr>
<td>(Increase)/decrease in long-term receivable</td>
<td>8</td>
<td>(1,354,082)</td>
</tr>
<tr>
<td>Unrealized foreign currency (gain)/loss</td>
<td></td>
<td>(346,649)</td>
</tr>
<tr>
<td>CASH FLOW FROM INVESTMENT ACTIVITY</td>
<td></td>
<td>14,048,942</td>
</tr>
<tr>
<td>CASH FLOW FROM INVESTMENT ACTIVITIES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Increase)/decrease in guarantees</td>
<td></td>
<td>(13,324)</td>
</tr>
<tr>
<td>(Increase)/decrease in derivative financial instruments</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Unrealized (gain)/loss on investment portfolio (Foundation Fund)</td>
<td>12</td>
<td>(32,073)</td>
</tr>
<tr>
<td>(Increase)/decrease in investment portfolio (Foundation Fund)</td>
<td>5</td>
<td>(14,399,252)</td>
</tr>
<tr>
<td>(Increase)/decrease in fixed assets</td>
<td>4</td>
<td>(177,583)</td>
</tr>
<tr>
<td>CASH FLOW RESULTING FROM INVESTMENT ACTIVITY</td>
<td></td>
<td>(14,622,232)</td>
</tr>
<tr>
<td>NET INCREASE/(DECREASE) OF CASH AND CASH EQUIVALENTS</td>
<td></td>
<td>(573,290)</td>
</tr>
<tr>
<td>Cash &amp; cash equivalents at beginning of year</td>
<td></td>
<td>57,409,733</td>
</tr>
<tr>
<td>Effect of exchange rate fluctuations on cash held</td>
<td></td>
<td>397,212</td>
</tr>
<tr>
<td>Cash &amp; cash equivalents at end of year</td>
<td></td>
<td>57,233,655</td>
</tr>
</tbody>
</table>
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS AS OF 31 DECEMBER 2018

1. GENERAL INFORMATION

a) Organization
MEDICINES FOR MALARIA VENTURE (MMV) is a Swiss foundation, established as a not-for-profit legal entity, registered in Geneva under statutes dated 15 November 1999. It is managed by a foundation council, a chief executive officer and eight senior managers.

With its head office in Geneva, the aim of MMV is to bring public and private sector partners together to fund, and provide managerial and logistical support, for the discovery and development of new medicines for the treatment and prevention of malaria. The products should be affordable and appropriate for use by populations in developing countries.

As with all Swiss foundations, Medicines for Malaria Venture is monitored by the Swiss Federal Supervisory Board for Foundations.

The consolidated financial statements for the year ending 31 December 2019 were approved for issue by the MMV Board on 24 March 2020.

b) Paid-in capital
The paid-in capital is fully subscribed at USD 4,000,000 as stipulated under the original legal statutes. Under normal circumstances, paid-in capital may be used during the year to meet cash flow shortfalls, but should be replenished before closing at year end. Paid-in capital together with the residual operating funds serves to maintain the viability of the organization, for 6 months, until other funding sources can be found.

c) Operation funds
The accumulated restricted and unrestricted operation funds represent the excess of core grants over expenditure since the inception of MMV. These funds are available to be utilized for future operations and project funding costs in accordance with the donors’ requirements.

d) Foundation Fund
In 2019, the MMV Board of Directors approved the establishment of a directly controlled quasi-endowment structure (the Foundation Fund, described in Note 5 below) to invest the revenues from the GSK Krintafel (tafenoquine) partnership described in Note 8 below, as well as any possible and similar future extraordinary revenue.

2. ACCOUNTING PRINCIPLES APPLIED IN THE PREPARATION OF THE FINANCIAL STATEMENTS

a) Basis of preparation
The consolidated financial statements have been prepared in accordance with the articles of incorporation of MMV, the applicable provisions of the Swiss Code of Obligations and the Swiss Generally Accepted Accounting Principles (Swiss GAAP FER/RPC), in particular RPC 21.

The consolidated financial statements have been prepared on a historical cost basis, except where a standard requires a different measurement basis.

Fair value is the amount for which a financial asset, liability or instrument could be exchanged between knowledgeable and willing parties in an arm’s length transaction.

The consolidated financial statements give a true and fair view of the organization’s financial position, the result of operations and cash flows.

Certain prior-year amounts have been reclassified to conform with the current year’s presentation.

b) Foreign currency translation
The consolidated financial statements are presented in US dollars (USD), since the majority of MMV’s activities are conducted in this currency (group functional and presentation currency).

Transactions in foreign currencies are translated at the foreign exchange rate ruling on the date of the transaction. Monetary assets and liabilities denominated in foreign currencies on the balance sheet date are translated to USD at the foreign exchange rate ruling on that date. Foreign exchange differences arising on translation are recognized in the consolidated statement of operations. Non-monetary assets and liabilities that are measured in terms of historical cost in a foreign currency are translated using the exchange rate on the date of the transaction.

c) Basis of consolidation
MMV has established a special purpose entity (SPE) for fundraising in North America (MMV, North America Inc.). MMV does not have any direct or indirect shareholdings in this entity. An SPE is consolidated if, based on an evaluation of the substance of its relationship with MMV and the SPE’s risks and rewards, MMV concludes it controls the SPE. The SPE is not fully controlled by MMV, but was established under such terms and conditions that it imposes strict limitations on the decision-making powers of the SPE’s management, with the result that MMV receives the majority of the benefits related to the SPE’s operations and net assets while being exposed to the majority of risks incident to the SPE’s activities, and retaining the majority of the residual or ownership risks related to the SPE or its assets. MMV appoints the board members of the SPE.

In accordance with Swiss GAAP FER 30 and based on the facts above, MMV North America Inc. is fully consolidated in these consolidated financial statements and has been, on a line by line basis, since 2011.

List of organizations consolidated in 2019:

<table>
<thead>
<tr>
<th>Country</th>
<th>Name and domicile</th>
<th>Functional currency</th>
<th>% controlled by MMV</th>
<th>Direct/Indirect</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States of America</td>
<td>MMV North America, Inc.</td>
<td>USD</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

All intra-group balances and transactions, and any unrealized gains and losses arising from intra-group transactions, are eliminated in preparing the consolidated financial statements.

d) Accounting estimates and judgements
The preparation of consolidated financial statements in conformity with Swiss GAAP FER requires management to make judgements, estimates and assumptions that affect the application of policies and reported amounts of assets and liabilities, income and expenditure. The estimates and associated assumptions are based on historical experience and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis of making the judgements about carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates. If, in the future, such estimates and assumptions, which are based on management’s best judgement on the date of the consolidated financial statements, deviate from the actual circumstances, the original estimates and assumptions will be modified as appropriate in the year in which the circumstances change.

Certain critical accounting judgements in applying MMV accounting policies are described below.
Revenue recognition
MMV enters into complex grant contracts that contain numerous provisions related to performance, reporting and spending. These criteria are monitored by both the scientific programme and finance teams to assess progress according to grant milestones and objectives. The evaluation of progress requires judgement, as it is based on subjective evaluations and discussions with programme participants and sponsors.

Research and development expenditure
MMV’s research and development expenditure is generally not direct expenditure, but is in the form of grants and contracts with external parties who perform certain tasks at their request. These requests are formalized by contracts and agreements that outline the requested services and development effort. Progress against expectations is difficult to measure, and measurement criteria are generally not defined in grant agreements. We review research plans and activities regularly to adjust annual funding levels prospectively. Additionally, actual research and development timing and execution are often different to that of the original plans. These factors lead to subjectivity in the timing and recognition of research and development expenditure.

3. CASH AND CASH EQUIVALENTS
Cash and cash equivalents comprise cash balances and short-term deposits with maturity of 1 month after the closing date.

<table>
<thead>
<tr>
<th></th>
<th>2019 USD</th>
<th>2018 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petty cash</td>
<td>10 265</td>
<td>6 685</td>
</tr>
<tr>
<td>Bank balances</td>
<td>40 129 307</td>
<td>37 403 048</td>
</tr>
<tr>
<td>Time deposits</td>
<td>17 094 083</td>
<td>20 000 000</td>
</tr>
<tr>
<td>Total cash and cash equivalents</td>
<td>57 233 655</td>
<td>57 409 733</td>
</tr>
</tbody>
</table>

4. FIXED ASSETS
Fixed assets are stated at cost less accumulated depreciation. Depreciation is charged to the consolidated statement of operations on a straight line basis over the estimated useful life of the assets.

- office furniture: 20%
- fixtures and installations: 33%
- computers and equipment: 33%

<table>
<thead>
<tr>
<th></th>
<th>Fixtures &amp; installations USD</th>
<th>Office furniture USD</th>
<th>Computers &amp; equipment USD</th>
<th>Total USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs at 1 January</td>
<td>905 996</td>
<td>397 210</td>
<td>415 844</td>
<td>1 719 050</td>
</tr>
<tr>
<td>Additions</td>
<td>118 044</td>
<td>3 238</td>
<td>57 142</td>
<td>178 424</td>
</tr>
<tr>
<td>Disposals</td>
<td>(4 900)</td>
<td>(8 086)</td>
<td>(184 949)</td>
<td>(198 776)</td>
</tr>
<tr>
<td>At 31 December</td>
<td>1 019 140</td>
<td>392 362</td>
<td>287 196</td>
<td>1 698 698</td>
</tr>
<tr>
<td>Accumulated depreciation at 1 January</td>
<td>800 132</td>
<td>390 611</td>
<td>352 754</td>
<td>1 543 497</td>
</tr>
<tr>
<td>Charge for the year</td>
<td>35 369</td>
<td>6 933</td>
<td>54 113</td>
<td>96 414</td>
</tr>
<tr>
<td>Disposals</td>
<td>(4 900)</td>
<td>(8 086)</td>
<td>(184 949)</td>
<td>(197 935)</td>
</tr>
<tr>
<td>At 31 December</td>
<td>830 601</td>
<td>389 458</td>
<td>221 918</td>
<td>1 441 976</td>
</tr>
<tr>
<td>Net book value at 31 December</td>
<td>188 539</td>
<td>2 904</td>
<td>65 278</td>
<td>256 722</td>
</tr>
</tbody>
</table>

5. INVESTMENT PORTFOLIO – FOUNDATION FUND
In 2019, the MMV Board of Directors approved the establishment of a directly controlled quasi-endowment structure (the Foundation Fund) to invest the revenues from the GSK Krintafel (tafenoquine) partnership described in Note 8 below, as well as any possible and similar future extraordinary revenue. The long-term strategic objective of the Foundation Fund is to improve the conditions for MMV business sustainability, and/or to pursue possible future opportunities, which are consistent with its humanitarian mission, but may be restricted by the current business model of the foundation. In 2019, the Board also approved the related investment policy and appointed an investment manager for the Foundation Fund, following a competitive selection process, and approved the transfer to the investment manager of the initial 50% received from GSK (described in Note 8). The investment of this initial amount is accounted for in MMV’s 2019 consolidated statement of financial position as a "long-term investment portfolio", as the intention of MMV is to keep these investments in the long run. In compliance with the investment policy approved by the Board, the above-mentioned assets were invested in:
- a discretionary fixed interest portfolio (USD-denominated, investment-grade bonds, 87.5% of total);
- a well-known exchange-traded fund, or ETF, (the MSCI World ESG Index) reflecting the performance of the global equity markets (10% of total); and
- a money market fund (2.5% of total).

The market value of this investment portfolio as of 31 December was the following:

<table>
<thead>
<tr>
<th></th>
<th>2019 USD</th>
<th>2018 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Money market funds</td>
<td>357 486</td>
<td>-</td>
</tr>
<tr>
<td>MSCI world environmental, social and governance index</td>
<td>1 480 020</td>
<td>-</td>
</tr>
<tr>
<td>Fixed interest portfolio (discretionary mandate)</td>
<td>12 593 819</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>14 431 325</td>
<td>-</td>
</tr>
</tbody>
</table>
6. SHORT-TERM PROVISIONS

A provision is recognized in the balance sheet when MMV has a present legal or constructive obligation as a result of a past event, and it is probable that an outflow of economic benefits will be required to settle the obligation.

<table>
<thead>
<tr>
<th></th>
<th>Unused vacation provision USD</th>
<th>Total provisions USD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Balance at 1 January 2018</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use/release</td>
<td>(599,954)</td>
<td>(599,954)</td>
</tr>
<tr>
<td>Allocation for the year</td>
<td>703,624</td>
<td>703,624</td>
</tr>
<tr>
<td><strong>Balance at 31 December 2018</strong></td>
<td>703,624</td>
<td>703,624</td>
</tr>
<tr>
<td>Use/release</td>
<td>(703,624)</td>
<td>(703,624)</td>
</tr>
<tr>
<td>Allocation for the year</td>
<td>838,540</td>
<td>838,540</td>
</tr>
<tr>
<td><strong>Balance at 31 December 2019</strong></td>
<td>838,540</td>
<td>838,540</td>
</tr>
</tbody>
</table>

7. REVENUE AND DONATIONS RECEIVABLE

Revenue recognition

Unrestricted grants

An unrestricted grant is recognized as revenue in the consolidated statement of operations when the grant becomes receivable. Any other grant which has performance, timing or other conditions is recognized in the balance sheet as revenue once the foundation has complied with the stipulated conditions. If the conditions have not yet been fully complied with, then this grant component is reported as a contingent asset as disclosed in Note 14.

At year end, if the unrestricted grants have not been fully used, they are presented as unrestricted operating funds in the balance sheet.

Restricted grants

When the donor wishes to see a donation allocated to a specific cause, the donation is considered to be a restricted grant. Restricted grants that have not been used at the end of the year are presented in the restricted operating funds in the balance sheet.

Contributions in-kind

Occasionally, MMV receives donations in kind, primarily in the form of free use of goods or services or preferential discounts. These in-kind contributions are not stated in the statement of operations as this type of contribution is difficult to valorize.

Below is a summary of donations received or committed during 2019:

<table>
<thead>
<tr>
<th></th>
<th>Cash received 2019</th>
<th>Revenue recognized during previous year</th>
<th>Donations receivable</th>
<th>Deferred revenue</th>
<th>Unrealized foreign exchange gain/(loss)</th>
<th>Total revenue as per statement of operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bill &amp; Melinda Gates Foundation (Core grant)</td>
<td>34,005,000</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>34,005,000</td>
</tr>
<tr>
<td>Bill &amp; Melinda Gates Foundation (Innovation Fund)</td>
<td>405,000</td>
<td>(405,000)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bill &amp; Melinda Gates Foundation (OMRI grant)</td>
<td>839,449</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>839,449</td>
</tr>
<tr>
<td>Bill &amp; Melinda Gates Foundation (QIMR grant)</td>
<td>506,839</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>506,839</td>
</tr>
<tr>
<td>Program for Appropriate Technology in Health (PATH, VivAccess grant)</td>
<td>488,750</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>488,750</td>
</tr>
<tr>
<td>Global Health Innovative Technology Fund (GHIT)</td>
<td>1,059,646</td>
<td>(81,200)</td>
<td>-</td>
<td>-</td>
<td></td>
<td>978,446</td>
</tr>
<tr>
<td>Swiss Agency for Development and Cooperation (DEZA/SDC)</td>
<td>1,619,726</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>1,619,726</td>
</tr>
<tr>
<td>Swiss Agency for Development and Cooperation (DEZA/SDC, Pregnancy registry)</td>
<td>634,216</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>634,216</td>
</tr>
<tr>
<td>UK Department for International Development (DFID)</td>
<td>23,290,080</td>
<td>(6,509,948)</td>
<td>-</td>
<td>-</td>
<td></td>
<td>16,780,132</td>
</tr>
<tr>
<td>United States Agency for International Development (USAID)</td>
<td>1,992,156</td>
<td>(6,509,319)</td>
<td>426,174</td>
<td>-</td>
<td></td>
<td>1,579,011</td>
</tr>
<tr>
<td>Irish Government Department of Foreign Affairs and Trade (Ishid)</td>
<td>1,118,822</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>1,118,822</td>
</tr>
<tr>
<td>Australian Government Department of Foreign Affairs and Trade (DFAT)</td>
<td>5,205,739</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>5,205,739</td>
</tr>
<tr>
<td>German Federal Ministry of Education and Research (BMBF)</td>
<td>1,860,923</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>1,860,923</td>
</tr>
<tr>
<td>Netherlands Development Cooperation (ODA)</td>
<td>3,842,671</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>3,842,671</td>
</tr>
<tr>
<td>Principality of Monaco Direction de la Coopération Internationale (DCI)</td>
<td>114,174</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>114,174</td>
</tr>
<tr>
<td>European and Developing Countries Clinical Trials Partnership (EDCTP, PAMAfrica grant)</td>
<td>9,793,333</td>
<td>-</td>
<td>(9,793,333)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unitaid (Supply grant)</td>
<td>974,516</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>974,516</td>
</tr>
<tr>
<td>Unitaid (VivAction grant)</td>
<td>124,800</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>124,800</td>
</tr>
<tr>
<td>Research Investment for Global Health Technology Fund (RIGHT Fund)</td>
<td>343,853</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>343,853</td>
</tr>
<tr>
<td>Newcrest Mining Limited</td>
<td>173,665</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>173,665</td>
</tr>
<tr>
<td>The MCJ Amelior Foundation</td>
<td>100,000</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>100,000</td>
</tr>
<tr>
<td>Individual donors</td>
<td>1,019</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>1,019</td>
</tr>
<tr>
<td><strong>TOTAL RECEIVED</strong></td>
<td>88,594,377</td>
<td>(7,835,467)</td>
<td>426,174</td>
<td>(9,793,333)</td>
<td></td>
<td>71,391,751</td>
</tr>
</tbody>
</table>

Of the total donations recognized in the consolidated statement of operations, USD 101,019 have been received through MMV North America Inc.
8. TOTAL OTHER REVENUE

Revenues from partnerships

Sanofi

MMV and pharmaceutical partner Sanofi have been collaborating for several years in the field of malaria, which is a key pillar of Sanofi’s global health strategy. Since 2011, MMV and Sanofi have been collaborating on the jointly funded development of novel malaria treatments combining artefenomel (OZ439) with a 4-aminoquinoline. Under this agreement, MMV-led activities related to an artefenomel/piperquine combination to the end of Phase II, while Sanofi led activities related to an artefenomel/ferroquine combination to the end of Phase II. MMV completed and terminated the artefenomel/piperquine programme in 2016 based on a futility analysis of the completed pivotal Phase Ib study. In December 2018, following changes in their strategy, Sanofi decided to stop all ongoing development activities in respect of the artefenomel/ferroquine drug combination programme and agreed upon the transfer to MMV of operational responsibility for the Phase II clinical studies in such a way that MMV would assume leadership, while Sanofi remained the sponsor of the studies, fulfilling drug supply and regulatory obligations. Accordingly, MMV and Sanofi agreed, in December 2018, that Sanofi would execute an indemnity payment of EUR 17,014,000 for the completion by MMV of the above-mentioned Phase II studies, from 1 January 2019 onwards. The parties further agreed that Sanofi’s obligations with respect to termination as per the existing agreement were fulfilled and that no further payments by Sanofi for activities beyond that date would be required. Therefore, MMV recognized the revenue associated with this indemnity payment (equivalent to USD 19,351,128) during fiscal year 2019.

In 2019, MMV decided to discontinue recruitment in the artefenomel/ferroquine phase IIb DR12805 (FALCI) study, since, based on an interim analysis, none of the tested doses showed sufficient efficacy according to pre-specified criteria in the protocol. MMV has nevertheless the obligation to bring the FALCI study to a compliant end. The parallel artefenomel/ferroquine ACT14655 Phase IIa study is also being completed as planned; however, irrespective of its outcome, it is very likely that the entire artefenomel/ferroquine development programme will be discontinued. MMV will take its final decision by July 2020, once all final results of both studies are available. A provision of USD 3,639,680 was booked at the end of fiscal year 2019 to account for the residual costs of the FALCI and ACT14655 activities from January to July 2020.

GlaxoSmithKline

MMV has been collaborating with pharmaceutical partner GlaxoSmithKline (GSK) on the co-development of Krintafel (tafenoquine) since 2008. On 20 July 2018, the United States Food and Drug Administration (FDA) granted regulatory approval, under priority review, of single-dose Krintafel for the radical cure (prevention of relapse) of Plasmodium vivax malaria, in patients aged 16 years and older, who are receiving appropriate antimalarial therapy for acute P. vivax infection. Under US law, following approval by the FDA of a treatment for a neglected or rare pediatric disease, the developer may receive a Priority Review Voucher (PRV) that entitles the recipient to a priority review by the FDA for a different drug. This voucher can either be used by the developer, or sold to a third party. Upon approval of Krintafel, the FDA granted a PRV to GSK. In October 2018, GSK used this PRV for a new drug application to the FDA by ViiV Healthcare, an affiliate of GSK. As the two parties had agreed that GSK would refund any additional expenditure incurred by MMV after 1 January 2019, by increasing the two residual payment amounts, MMV recognized USD 1,354,081 as revenue from the GSK partnership during fiscal year 2019. MMV also increased the long-term receivable by the same amount, so that the total of the two residual payments due in July 2022 and July 2023 increased to USD 15,567,566 (2018: USD 14,213,484). The Krintafel trademark is owned by/licensed to the GSK group of companies.

Others

In 2019, in addition to the above-mentioned USD 1,354,081 revenue from the GSK partnership (refund of additional Krintafel co-development expenditure), MMV booked the following revenues from partnerships: USD 1,028,556 from Janssen in respect of the co-development of P218 and IM-atovaquone (2018: USD 531,989), and USD 180,123 from Shin Poong (2018: USD 445,697). In 2018 MMV had also received USD 2,000,000 from Takeda in respect of the co-development of DSM265 and USD 779,818 from Sanofi in respect of the co-development of OZ439/ferroquine. MMV plans to use the above-mentioned revenues from partnerships in support of its charitable mission.

All other types of revenues which are not considered as donations are presented in other unrestricted revenues as follows:

<table>
<thead>
<tr>
<th></th>
<th>2019</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>USD</td>
<td>USD</td>
</tr>
<tr>
<td>Tax at source commission</td>
<td>37,059</td>
<td>33,578</td>
</tr>
<tr>
<td>Event sponsorship</td>
<td>-</td>
<td>21,303</td>
</tr>
<tr>
<td>Honorarium</td>
<td>32,771</td>
<td>32,002</td>
</tr>
<tr>
<td>Consulting fees</td>
<td>17,952</td>
<td>-</td>
</tr>
<tr>
<td>Reimbursement from grantees</td>
<td>30,692</td>
<td>14,208</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>53,456</td>
</tr>
<tr>
<td><strong>OTHER INCOME</strong></td>
<td><strong>118,474</strong></td>
<td><strong>154,547</strong></td>
</tr>
</tbody>
</table>
9. DEFERRED REVENUE
In late December 2019, MMV received the first payment from the European and Developing Countries Clinical Trials Partnership (EDCTP) as a pre-financing grant equivalent of USD 9,793,333. Considering the grant agreement defines the starting date of the project as 1 January 2020, this payment was recognized as deferred revenue and will be booked as revenue in fiscal year 2020.

In 2018 a deferred revenue of USD 19,470,549 was recorded in respect of the indemnity payment received from Sanofi as described in Note 8 and its employees.

10. PROJECT GRANTS
Expenditure and grants allocated for research and development activities undertaken with the prospect of gaining new scientific or technical knowledge and understanding are recorded on the basis of contracts with grantees. In the event that a portion of a grant is unpaid at the year end, it is included under current liabilities. Expenses paid before year end for the following period are recorded as prepaid portfolio commitments.

Regulatory and other uncertainties inherent in the development of new products in this sector preclude MMV from capitalizing on development costs.

Project reimbursements receivable
These refer to unused balances of project grants previously committed, which are returned to MMV by the project partners as stipulated in the individual contractual agreements on termination or reorganization of R&D projects.

11. PERSONNEL EXPENSES
Salaries and related charges are included under project expenditure and support of portfolio expenditure in the consolidated statement of operations.

As of 31 December 2019 there were 60.7 full-time equivalent employees with permanent contract at 31 December 2019 (2018: 59.2), as well as 42.6 full-time equivalent temporary staff members with fixed-term contract ranging between 1 and 3 years (2018: 30.8).

The pension plan covers all employees for death and disability benefits. Cover for retirement benefits begins in the year following each employee’s 24th birthday. The retirement pension is based on the level of the retirement credits, the interest rate to be credited and the conversion rate to be applied at retirement age. Risk benefits are related to pensionable salary.

The occupational benefits are provided by a collective foundation, Profond, according to a defined contribution benefit plan: investment yield has no impact on premiums; the employer does not guarantee the benefit amount. The plan is funded by the contribution of MMV and the employees.

<table>
<thead>
<tr>
<th></th>
<th>2019 USD</th>
<th>2018 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capital ratio</td>
<td>111.3%</td>
<td>103.0%</td>
</tr>
<tr>
<td>Amount payable to pension fund</td>
<td>1,999</td>
<td>43</td>
</tr>
</tbody>
</table>

12. FINANCIAL RESULT

<table>
<thead>
<tr>
<th></th>
<th>2019 USD</th>
<th>2018 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derivatives fluctuation</td>
<td>-</td>
<td>30,670</td>
</tr>
<tr>
<td>Unrealized gain on portfolio investments</td>
<td>32,073</td>
<td>-</td>
</tr>
<tr>
<td>Bank interests</td>
<td>764,401</td>
<td>151,722</td>
</tr>
<tr>
<td>Exchange gain from CHF</td>
<td>147,333</td>
<td>-</td>
</tr>
<tr>
<td>Exchange gain from EUR</td>
<td>49,962</td>
<td>88,390</td>
</tr>
<tr>
<td>Exchange gain from GBP</td>
<td>11,263</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>1,005,032</td>
<td>270,782</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2019 USD</th>
<th>2018 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derivatives fluctuation</td>
<td>-</td>
<td>164,163</td>
</tr>
<tr>
<td>Bank charges</td>
<td>47,412</td>
<td>40,303</td>
</tr>
<tr>
<td>Exchange loss from CHF</td>
<td>-</td>
<td>121,179</td>
</tr>
<tr>
<td>Exchange loss from GBP</td>
<td>-</td>
<td>292,523</td>
</tr>
<tr>
<td>Exchange loss from AUD</td>
<td>131,831</td>
<td>204,282</td>
</tr>
<tr>
<td>Total</td>
<td>179,243</td>
<td>822,450</td>
</tr>
</tbody>
</table>

13. LEASES
Non-cancellable operating lease rentals are payable as follows:

<table>
<thead>
<tr>
<th></th>
<th>2019 USD</th>
<th>2018 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 year</td>
<td>1,068,427</td>
<td>947,688</td>
</tr>
<tr>
<td>Between 1 and 5 years</td>
<td>3,880,854</td>
<td>4,381,325</td>
</tr>
<tr>
<td>More than 5 years</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>4,949,281</td>
<td>5,329,013</td>
</tr>
</tbody>
</table>

In order to minimize the potential adverse effect of foreign exchange fluctuations, the MMV liquidity is deposited in bank accounts denominated in foreign currencies pro rata to the breakdown of total expenditure by currency (natural hedging).

MMV has several operating leases. These leases generally run for a period of 6 years, with an option to renew the lease after that date. During the year ended 31 December 2019, USD 794,236 was recognized as an expense in the consolidated statement of operations in respect of operating leases (2018: USD 973,961).
14. CONTINGENT ASSETS
As per current contractual agreements, and depending on satisfactory reporting to donors, contingent assets related to donations are as follows:

<table>
<thead>
<tr>
<th></th>
<th>2019 USD</th>
<th>2018 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 year</td>
<td>70,274,379</td>
<td>68,630,204</td>
</tr>
<tr>
<td>Between 1 and 5 years</td>
<td>165,956,820</td>
<td>191,652,466</td>
</tr>
<tr>
<td>More than 5 years</td>
<td>-</td>
<td>18,400,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>236,231,199</td>
<td>278,682,670</td>
</tr>
</tbody>
</table>

15. RELATED PARTIES
MMV has a related-party relationship with its board members, executive officers and MMV North America Inc.

Board members serve on a voluntary basis and receive no remuneration. They are compensated for travel and accommodation for participation in board meetings and receive a per diem allowance to cover incidental expenses during these events.

<table>
<thead>
<tr>
<th></th>
<th>2019 USD</th>
<th>2018 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Board members &amp; meetings</td>
<td>329,817</td>
<td>349,639</td>
</tr>
</tbody>
</table>

There were no loans to directors or executive officers for the years ended 31 December 2019 and 31 December 2018.

Some donors are represented in the foundation council. Given the foregoing, these donors could be considered as related parties. However, MMV management considers that their presence in the foundation council does not affect the nature of the relation between MMV and these donors.

Therefore, all MMV donors have been considered third parties.

16. RISK MANAGEMENT
The foundation council has overall responsibility for organizing and supervising risk management. The audit committee monitors management’s approach to risk management in compliance with the organization’s principles and procedures and verifies that risks are managed appropriately in light of the current risks faced by the organization. Based on a risk identification carried out periodically, MMV’s essential risks are assessed in respect of likelihood and impact and documented in a risk analysis report. The management has the responsibility to monitor and supervise the substantial risks.

For risks related to accounting principles and financial reporting, a risk analysis was carried out. Controls in line with the internal control system have been defined and measures resulting from this have been implemented in order to minimize the risks related to accounting principles and financial reporting.

17. GUARANTEES
Guarantees concern office rental only and are recoverable on vacating the premises subject to the prevailing contracts.

18. CAPITAL COMMITMENTS AND CONTINGENCIES
MMV encounters certain risks and uncertainties in conducting its work. These risks and uncertainties have financial statement implications. In all instances, these have been considered in the consolidated financial statements, despite the fact that the outcomes of these uncertainties cannot be predicted with absolute certainty. Management has concluded that provisions for these risks are appropriate, and any adverse resolution of these uncertainties will not have a material impact on the financial position or results of the foundation.

19. AUDITORS
KPMG SA, Geneva, have been MMV’s statutory auditors since the fiscal year 2003. Following a competitive bid in 2017, KPMG were reappointed as the statutory auditors. The current lead auditor, Hélène BEGUIN, has acted in this capacity since 2017.

During the fiscal year 2019, MMV paid a total of USD 96,890 (2018: USD 103,933) to its auditors. This amount can be split as follows:

- Audit services (including special audit reports to donors): USD 96,890 (2018: USD 91,444)
- Other services: nil (2018: USD 12,389)

20. SUBSEQUENT EVENTS
It is acknowledged that the COVID-19 pandemic will likely have significant impact on the feasibility of certain core operational activities of MMV, primarily the conduct of clinical studies. There are also risks regarding the provision of donor funding being delayed or withheld. To mitigate these risks, the organization is currently identifying projects that will be delayed. It is also in contact with the donors supporting those projects. MMV has already observed that its expertise in drug R&D, manufacturing and access will be of value in the global effort against COVID-19. In order to support that work, MMV will discuss with donors the allocation and funding for COVID-19 support.
Behind the scenes 2019

MMV Board

Mr Per Wold-Olsen
Chairman of MMV Board; former President of Human Health Intercontinental Region, Merck & Co., Inc., Middle East & Africa; former Member of Merck’s Management Committee; Chairman GN Store Nord A/S, Denmark; Board Member of Gilead Sciences Inc., USA; Chair of Oncopeptides AB, Sweden

Dr David Brandling-Bennett
Former Senior Advisor, Malaria, Bill & Melinda Gates Foundation, USA

Mr Alan Court
Senior Adviser to the WHO Ambassador for Global Strategy, USA; former Director of the UNICEF Programme Division in New York; former Director of the UNICEF Supply Division in Copenhagen

Prof. Sir Michael Ferguson
Regius Professor of Life Sciences and Associate Dean for Research Strategy, University of Dundee, Scotland, UK

Dr Winston Gutteridge
Former Chief, Product R&D, Special Programme for Research and Training in Tropical Diseases (TDR), World Health Organization, Switzerland

Ms Yuli Ismartono
Co-founder and Managing Editor of AsiaViews; formerly with TEMPO magazine; Board Member of Nature Resources Governance Institute; the Coral Triangle Center; the Prestasi Junior Indonesia; and the Alternative Association of Southeast Asian Nations, Indonesia

Mr Gabriel Jaramillo
Former General Manager of the Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland

Dr Dominique Limet
Former Chief Executive Officer, ViiV Healthcare, London, UK

Ms Elizabeth Linder
Executive Director, Beautiful Destinations, Senior Consulting Fellow, Chatham House Director’s Office; former Politics & Government Specialist, Facebook (California and EMEA region), based in USA/UK

Dr Robert Newman
Director, Aspen Management Partnership for Health, The Aspen Institute; Former Vice President and Global Head, TB Programs, Johnson & Johnson; former Director of Global Malaria Programme, WHO

Dr Dominique Limet
Former Chief Executive Officer, ViiV Healthcare, London, UK

Ms Joy Phumaphi
Co-Chair of the Independent Expert Review Group for Every Woman Every Child; Chair of the Global Leaders Council for Reproductive Health; Executive Secretary of African Leaders Malaria Alliance, USA

Dr David Reddy
CEO, MMV, Switzerland

Dr Wendy Sanhai
Deloitte Consulting, LLP (Federal Strategy and Operations); Associate Professor (adj), Duke University, School of Medicine; former Senior Scientific Advisor, Office of the Commissioner, US Food and Drug Administration; former Senior Director, Global Regulatory Affairs, GSK, USA

Ambassador
Dr Konji Sebati
CEO, Innovative Pharmaceutical Association of South Africa (IPASA), Johannesburg, South Africa

Dr Dennis Schmatz
Former Vice President and Head of Tsukuba Research Institute, Merck-Banyu Research Laboratories, Japan (now based in USA)

* Members of the Audit & Finance Committee  ** Chair of the Audit & Finance Committee

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Expert Scientific Advisory Committee (ESAC)

Dr John Pottage
Co-Chairman MMV ESAC
(Drug Development); Chief
Scientific and Medical Officer,
ViiV Healthcare, USA

Dr Michael Witty
Co-Chairman MMV ESAC
(Drug Discovery); Drug
Discovery Consultant and
former Vice President Pfizer
R&D, UK

Dr Aileen Allsop
Former Vice President for
Science Policy, R&D,
AstraZeneca, UK

Prof. Thomas Baillie
Dean Emeritus, School of
Pharmacy, University of
Washington, USA

Dr Tesfaye Biftu
Distinguished Professor, National Institute of
Pharmaceutical Sciences,
Addama Science and
Technology University, Ethiopia

Sir Simon Campbell
Former Senior Vice President
for WW Discovery, Pfizer,
organic chemist, UK

Dr Anne Cooper
Programme Director,
Sosei Heptanes, UK

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Chemistry, University of
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Sciences, UK

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CEO, Safety Monitoring &
Clinical Trials Division, Food
and Drugs Authority, Ghana

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Chief Medical Officer,
Durata Therapeutics, USA

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Professor and Co-Chief,
Division of Infectious
Diseases, Department of
Medicine, Washington
University, USA

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Preclinical Safety Consultant
at Preclinical Safety
Consulting Ltd, UK

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Eimunjeze
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Administration and Control,
Nigeria

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by Nestlé Skin Health/
Galderma R&D, Sophia
Antipolis, France

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Georgia, USA

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Fiocruz, Brazil

Prof. John Lambert
Chief Medical Officer, Global
Head Medical Affairs and
Consulting, PAREXEL
International – Early Phase
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Research Fellow, Discovery
Chemistry Research and
Technologies, Eli Lilly and
Company, USA

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KGM Pharma Consulting
LLC, USA

Dr Robert Riley
Executive Vice President,
Drug Discovery, Evotec, UK

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Mariña Health Research
Centre, Mozambique

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Director, Australian Defence
Force Malaria and Infectious
Diseases Institute, Australia

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Sieg Pharma Consulting,
USA

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President’s Malaria Initiative,
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Coordinator the Malaria
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FACT Medical Coordinator,
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Boehringer Foundation,
Switzerland

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Malaria Expert on Global
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former Director NMCP;
Rwanda

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Supply Chain Expert,
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Biochemistry, University of
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Independent Consultant in
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Medicine, Sri Lanka

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Centre, The Graduate
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Pharmaceutical Preclinical
Safety Consultant, UK

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Health Research (Australia),
Professor of Tropical
Medicine at the Centre of
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University of Oxford, UK

Dr Melanie Renshaw
Chief Technical Advisor,
ALMA, and Co-Chair, Roll
Back Malaria CRSPC,
Switzerland

Dr Frank Richards Jr.
M.D. Director, River
Blindness Elimination
Program, Lymphatic
Filariasis Elimination
Program, and
Schistosomiasis Control
Program, Carter Center,
USA

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Vice-Chairman of MMV
APMAC; Chief, Global Drug
Facility, Stop TB Partnership,
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Access & Product Management Advisory Committee (APMAC)

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USA

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USA

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Vice-Chairman of MMV
APMAC; Chief, Global Drug
Facility, Stop TB Partnership,
Switzerland

Global Safety Board (GSB)

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Co-Chairman MMV Global
Safety Board; Chief Medical
Officer, MMV, Switzerland

Dr Trevor Gibbs
Co-Chairman MMV Global
Safety Board; Independent
Consultant; former
Senior Vice President,
Pharmacovigilance &
Medical Governance,
GSK, UK

Prof. Tim Hammond
Pharmaceutical Preclinical
Safety Consultant, UK

Prof. Pieter Joubert
Clinical Pharmacology
Consultant, UK

Dr John Pears
Director, Woodhouse
Green, UK

Ms Andrea Lucard
Executive Vice President,
Corporate Affairs,
MMV, Switzerland

Dr Dennis Schmatz
Former Vice President and
Head of Tsukuba Research
Institute, Merck-Banyu
Research Laboratories,
Japan (now based in USA)
MMV is grateful for the support received from the following institutional donors:

- **Australian Government**
- **Department of Foreign Affairs and Trade**
- **Federal Ministry of Education and Research**
- **Gouvernement Prinçier PRINCIPAUTÉ DE MONACO**
- **The MCJ Amelior Foundation**
- **NEWCREST MINING LIMITED**
- **RIGHTFUND**
- **UKaid**
- **USAID**
- **Unitaid**

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