Discover Tanin’s story on p. 29
Malaria
- takes a child’s life every 2 minutes
- kills an estimated 435,000 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.

MMV Disclaimer
This document contains certain forward-looking statements that may be identified by words such as ‘believes’, ‘expects’, ‘anticipates’, ‘projects’, ‘intends’, ‘should’, ‘seeks’, ‘estimates’, ‘future’ or similar expressions, or by discussion of, among other things, vision, strategy, goals, plans, or intentions. It contains hypothetical future product target profiles, development timelines and approval/launch dates, positioning statements, claims and actions for which the relevant data may still need to be established. Stated or implied strategies and action items may be implemented only upon receipt of approvals including, but not limited to, local institutional review board approvals, local regulatory approvals, and following local laws and regulations. Thus, actual results, performances or events may differ from those expressed or implied by such statements. We ask you not to rely unduly on these statements. Such forward-looking statements reflect the current views of Medicines for Malaria Venture (MMV) and its partners regarding future events, and involve known and unknown risks and uncertainties.

MMV accepts no liability for the information presented here, nor for the consequences of any actions taken on the basis of this information. Furthermore, MMV accepts no liability for the decisions made by its pharmaceutical partners, the impact of any of their decisions, their earnings and their financial status.

© June 2019 Medicines for Malaria Venture
All rights are reserved by Medicines for Malaria Venture. The document may be freely reviewed and abstracted, with a clear and appropriate acknowledgement of source, but is not for sale or for use in conjunction with commercial purposes. Requests for permission to reproduce or translate the document, in part or in full, should be addressed to the administration of Medicines for Malaria Venture, where information on any translation or reprints is centralized.
# Contents

<table>
<thead>
<tr>
<th>Destination eradication: smarter moves in a shifting landscape</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Taking aim at malaria: a target-based approach to drug design</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Improving case management of uncomplicated malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
</tr>
<tr>
<td>13</td>
</tr>
<tr>
<td>14</td>
</tr>
<tr>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Accelerating access to severe malaria interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
</tr>
<tr>
<td>21</td>
</tr>
<tr>
<td>22</td>
</tr>
<tr>
<td>23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Next-generation tools to tackle relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
</tr>
<tr>
<td>27</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protecting the most vulnerable</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
</tr>
<tr>
<td>28</td>
</tr>
<tr>
<td>29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R&amp;D platforms and discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
</tr>
<tr>
<td>32</td>
</tr>
<tr>
<td>33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Financial view</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Behind the scenes</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
</tr>
</tbody>
</table>
What a difference 20 years of partnership makes. In 1999, when MMV and its partners made a commitment to fill the empty malaria R&D pipeline, around one million people were losing their lives to the disease. Since then, as the global health community works towards the goal of eradication, the 10 medicines brought forward by MMV and partners have contributed to saving almost 2 million lives from malaria, mostly young children.

Yet the malaria parasite is fiercely tenacious. Despite a 60% drop in malaria deaths between 2000 and 2015, the World Malaria Report 2018 describes a slowing in progress to reduce malaria cases between 2015 and 2017. Around 435,000 people continue to lose their lives to malaria each year.

In light of this, in 2018, the malaria community, including MMV, reassessed their strategies to understand why progress is levelling off and what else can be done to win the fight against this disease. In response, in 2018 the World Health Organization (WHO) and partners launched the “High burden to high impact” initiative, a country-led approach which aims to accelerate much-needed progress against malaria focusing on 11 countries that account for approximately 70% of the global malaria burden, 10 on the African continent plus India.

A focus on children – the most vulnerable

Seven out of every ten malaria deaths are those of a child under the age of 5. We want all children in eligible malaria-endemic areas to benefit from seasonal malaria chemoprevention (SMC). Last year, 81 million monthly courses of SMC (sulfadoxine-pyrimethamine plus amodiaquine) were shipped – enough to reach more than 20 million children. MMV has also launched a new programme known as SEAMACE (SEAsonal MAria Chemoprevention Extension) to explore smarter ways of reaching even more children living at risk of malaria.

Furthermore, we are working to ensure that no child faces disability or death from severe malaria because they were unable to reach a healthcare facility in time. Two MMV-supported rectal artesunate suppositories (RAS) products, from Cipla and Strides Shasun, both prequalified by the WHO last year, are being rolled out in programmes designed to ensure their timely and correct use. In this context, RAS is buying valuable time for afflicted children to receive the follow-on care they need.

MAMaZ Against Malaria, an MMV-supported project in the rural Serenje District of Zambia, highlights the significant impact these suppositories can have. Led by a consortium of partners including Transaid, the National Malaria Elimination Centre in Zambia and MMV, the project saw children with suspected severe malaria receive RAS before being transported by bicycle ambulance to facilities for treatment with injectable artesunate. In 12 months, severe-malaria case fatality was reduced by an impressive 96%. On the back of these results and thanks to funding from Grand Challenges Canada and the Government of Canada, the consortium will be able to scale up the project to benefit four times as many people in rural Zambia.

New medicines

Meanwhile, 2018 saw 10 years of development work, in partnership with GlaxoSmithKline (GSK), bear fruit – tafenoquine (Krintafel/Kozenix®), was approved both by the US Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration (TGA).
With these approvals, tafenoquine became the first new medicine for the radical cure of relapsing Plasmodium vivax malaria in more than 60 years. For endemic countries, for example in Southeast Asia and Latin America, this marks a major milestone on the road to malaria eradication.

Behind this, our portfolio of next-generation medicines – designed to meet the unmet medical needs of malaria patients in the highest burden countries – is robust and growing stronger. Ten compounds or combinations are in clinical trials today. In one example, MMV in partnership with Novartis have progressed ganaplacide combined with a new formulation of lumefantrine through Phase IIb and results of the interim analysis are promising. Furthermore, the combination is already being formulated to address the needs of children.

New drug discovery

Meanwhile, MMV’s drug discovery engine delivered a steady stream of new potential product candidates. New tools, from liver assays to volunteer infection studies and preclinical models, are providing us with a breadth and depth of information on these new previously inaccessible candidates. Armed with this information, we can get smarter not only in our efforts to identify new compound series for the treatment of malaria but also in the selection of compounds for combinations. Furthermore, these tools and data guide the identification of compounds for relapse prevention, transmission blocking and the protection of vulnerable populations – essential characteristics of the medicines needed for elimination and eradication.

Looking ahead

Twenty years ago, we laid an important cornerstone in the foundation to build a world free from malaria. The next 20 years will be just as critical as some countries move towards elimination and the malaria community works to turn the tide for high burden countries. As WHO Director-General Dr Tedros Adhanom Ghebreyesus told the 71st World Health Assembly: “We must act with a sense of urgency in everything we do, because every moment we lose is a matter of life and death.” It is with this urgency that MMV will pursue the parallel tracks of facilitating access to antimalarials for high burden countries today while developing the tools needed tomorrow for the elimination and eventual eradication of malaria.

We would like to thank all our partners – past, present and future – who join us in this mission. We thank, too, the board and donors for their unstinting support, and our staff for their passion, commitment and hard work. And we urge you all to continue with us on our journey to destination eradication.


2 Trademarks owned or licensed by GSK
Key achievements 2018

1.9 million lives saved by MMV-supported antimalarials since 2009

96% reduction in severe malaria case fatality demonstrated in a pilot project to expand access to life-saving medicine in Zambia led by a consortium of partners including Transaid, the Zambia National Malaria Elimination Center and MMV.

10th MMV-supported medicine:
Strides Pharma Science's rectal artesunate product (Artecap™) received WHO prequalification

1st new medicine
for the radical cure of relapsing *P. vivax* malaria in more than 60 years, tafenoquine developed with GSK, approved by the US FDA (*Krintafel*) and the Australian TGA (*Kozenis*).

2nd manufacturer
of injectable artemisinate secured – Ipca received WHO prequalification in Dec 2018 for Larinate® 60

10 compounds
in clinical development with the potential to become medicines for children, pregnant women and people suffering from drug-resistant malaria.

1 donor dollar
creates an estimated 3.5 dollars of investment impact thanks to direct and in-kind support from our partners.
385 million treatments
of child-friendly ACT Coartem® Dispersible (artemether-lumefantrine, developed with Novartis) distributed to more than 50 countries since 2009 — a volume MMV estimates to have saved around 825,000 lives

128 million vials
of Artesun® (injectable artesunate) delivered by Fosun Pharma since 2010 for severe malaria, saving an estimated 840,000 additional lives compared with quinine treatment

84% of patients
recruited in CANTAM* study to investigate the real-life safety and tolerability of Pyramax® (pyronaridine-artesunate, developed with Shin Poong) in Central Africa and Ivory Coast

81 million courses
of seasonal malaria chemoprevention shipped to countries in the Sahel in 2018, enough to protect 20 million children

319 Pathogen Boxes
shipped to scientists around the world free of charge by year end — catalysing drug discovery for neglected diseases

385 million treatments
of child-friendly ACT Coartem® Dispersible (artemether-lumefantrine, developed with Novartis) distributed to more than 50 countries since 2009 — a volume MMV estimates to have saved around 825,000 lives

128 million vials
of Artesun® (injectable artesunate) delivered by Fosun Pharma since 2010 for severe malaria, saving an estimated 840,000 additional lives compared with quinine treatment

84% of patients
recruited in CANTAM* study to investigate the real-life safety and tolerability of Pyramax® (pyronaridine-artesunate, developed with Shin Poong) in Central Africa and Ivory Coast

81 million courses
of seasonal malaria chemoprevention shipped to countries in the Sahel in 2018, enough to protect 20 million children

319 Pathogen Boxes
shipped to scientists around the world free of charge by year end — catalysing drug discovery for neglected diseases

385 million treatments
of child-friendly ACT Coartem® Dispersible (artemether-lumefantrine, developed with Novartis) distributed to more than 50 countries since 2009 — a volume MMV estimates to have saved around 825,000 lives

128 million vials
of Artesun® (injectable artesunate) delivered by Fosun Pharma since 2010 for severe malaria, saving an estimated 840,000 additional lives compared with quinine treatment

84% of patients
recruited in CANTAM* study to investigate the real-life safety and tolerability of Pyramax® (pyronaridine-artesunate, developed with Shin Poong) in Central Africa and Ivory Coast

81 million courses
of seasonal malaria chemoprevention shipped to countries in the Sahel in 2018, enough to protect 20 million children

319 Pathogen Boxes
shipped to scientists around the world free of charge by year end — catalysing drug discovery for neglected diseases

40 chemical series
being optimized towards preclinical candidates and 3 new antimalarial candidates delivered in 2018

150 active partners
working to help defeat malaria — part of an overall network of 400 partners in 55 countries

30,000 compounds screened
in P. vivax liver-stage assays led to the identification of several potential radical cure hits, with one series currently undergoing early optimization

* CANTAM: Central African Network on Tuberculosis, HIV/AIDS and Malaria
Strategic focus

In line with global frameworks from the WHO and the United Nations, MMV is focused on facilitating access to current antimalarials, particularly in high-burden countries, while researching and developing the next generation of medicines needed for the elimination and eventual eradication of malaria.

To facilitate access, MMV works with partners and key global and country-level stakeholders to gather data on the tolerability of new medicines, specifically in vulnerable populations and in “real-world” settings. This evidence supports their adoption into relevant national policies and guidelines. These efforts also include securing sustainable supply, by diversifying the manufacturing base of existing medicines and scaling up use.

In its research and development (R&D) efforts, MMV focuses on the need for accelerated, efficient and appropriate drug discovery and development using a range of supportive research tools, including assays (p. 27), models and platforms (pp. 30–32). Given the 12 to 15 year timeline from discovery to launch of a new medicine, it is important to invest in only those promising compounds that can potentially satisfy identified unmet medical needs. This is described by two target product profiles (TPPs).

TPP1 defines the characteristics of drugs for treatment of uncomplicated malaria by targeting the blood-stage infection. The ultimate goal is to overcome resistance and shorten the treatment course. Such a drug may also provide post-treatment protection and block transmission. In the best case it would be what is known as a single exposure radical cure and prophylaxis (SERCaP). Simplifying case management would thus help improve compliance. MMV also reviews all molecules for potential to provide new injectable treatments for severe malaria.

TPP2 describes drugs to protect vulnerable populations, such as non-infected people entering an area of high malaria endemicity, or children already living in areas of high endemicity. This is described as single exposure prophylaxis and would always include one molecule active against the liver stages of malaria. To reduce the risk of drug resistance emerging, for a given geographic area, combinations used for protection should have different active ingredients from those used to cure malaria.

The development of a new treatment for uncomplicated malaria or a new prophylactic regimen requires the combination of at least two active candidate drugs. MMV has defined five target candidate profiles (TCPs) corresponding to different clinical attributes needed for combination to meet the TPPs (Figure 1). Two types of molecules MMV screens for are those which stop transmission, either by killing the parasite in the human host, or in the mosquito. A final group are those which prevent relapse of the dormant forms of *P. vivax*, which is a critical part of malaria eradication. Central to everything is that all new molecules must be able to overcome existing clinical resistance, and are tested for their robustness against generating resistance in the future.

MMV is currently working with more than 150 partners around the world on its portfolio of R&D and access projects. Together with partners, MMV will continue to optimize the discovery, development and delivery of new antimalarials to help control and ultimately eradicate malaria.

Figure 1: Linking the TPPs to the TCPs

---

## MMV-supported projects

| Research | Candidate profiling | Translational | Human volunteers | Product development | Regulatory review | Access
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Miniportfolio</td>
<td>GSK</td>
<td>Pantothenates</td>
<td>Zydus Cadila</td>
<td>MMV253</td>
<td>Artefenomel/ferroquine</td>
<td>Sanofi</td>
</tr>
<tr>
<td>Phenotypic lead</td>
<td>Daiichi-Sankyo</td>
<td>SAR121</td>
<td>Sanofi</td>
<td>SJ733</td>
<td>Ganaplcide/lumefantrine</td>
<td>Novartis</td>
</tr>
<tr>
<td>Open Source Series</td>
<td>Univ. of Sydney</td>
<td>MMV370 MMV371</td>
<td>Merck KGaA</td>
<td>M5717</td>
<td>Cipargamin</td>
<td>Novartis</td>
</tr>
<tr>
<td>Phe tRNA ligase</td>
<td>Broad Institute/Eisai</td>
<td>MMV052</td>
<td>Takeda</td>
<td>DSM265</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purines</td>
<td>Celgene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GWT1</td>
<td>Eisai</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular target</td>
<td>Drug Discovery Unit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azabenzimidazole</td>
<td>UNCAMP, Univ. of Campinas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miniportfolio</td>
<td>Novartis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SJ733 backup</td>
<td>Univ. of Kentucky</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenotypic lead</td>
<td>Sanofi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHODH</td>
<td>Univ. of Texas Southwestern/ Univ. of Washington/ Monash Univ.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenotypic lead</td>
<td>Univ. of Cape Town</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-muscular</td>
<td>Calibra</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Target product profiles

- **3-day cure, artemisinin-based combination therapies**
- **Uncomplicated malaria treatments aiming at a new single-exposure radical cure (SERC) TPP-1**
- **Intermittent/seasonal malaria chemoprevention**
- **Severe malaria treatment/pre-referral intervention**
- **Products targeting prevention of relapse for *P. vivax***
- **Single-exposure prophylaxis TPP-2**


### To develop the individual compounds for combination in the TPPs, MMV has defined five target candidate profiles (TCPs):

- **Blood-stage killers** (TCP 1)
  - Hypnozoite killers (anti-relapse)
- **Prophylaxis** (TCP 2)
- **Transmission blockers** (TCP 3)
- **Paediatric formulation** (TCP 4)
- **WHO prequalified OR approved/positive opinion by regulatory bodies who are ICH* members/observers**

- **Brought into portfolio after approval and/or development**
- **Global Fund Expert Review Panel reviewed product – permitted for time-limited procurement, while regulatory/WHO prequalification review is ongoing**

*International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use*
Taking aim at malaria:

a target-based approach
to drug design

MMV's Project of the Year 2018 is awarded to a discovery team led by Prof. Ian Gilbert, Prof. Kevin Read and Dr Beatriz Baragaña at the Drug Discovery Unit (DDU), University of Dundee, UK. Working alongside Dr Paul Willis and Delphine Baud at MMV, as well as Sir Simon Campbell, of MMV’s Expert Scientific Advisory Committee, the project team have identified an exciting new compound series, active against a novel biological target – Plasmodium falciparum’s enzyme lysyl-tRNA synthetase (PfKRS1).

In the early phases of malaria drug discovery, scientists use validated assays to perform two types of screening – phenotypic or target-based. In phenotypic screening, the aim is simply to identify compound series that kill the parasite, even if the exact mechanism of action is unknown. Over the last decade, MMV has identified the majority of its compounds this way. A more focused approach, however, is target-based screening, which aims to identify compound series that can inhibit specific biological processes or molecules that are known to be effective treatment targets. This approach, which has proved successful in many therapy areas, brings together complementary methodologies (including structural biology, computational chemistry, molecular biology and biochemistry). It also builds on existing knowledge, where available – such as the structure of a binding site – to inform and expedite drug design. The initial challenge with the target-based approach, however, is identifying a good drug target.

At present, there are relatively few validated targets in the malaria parasite. The discovery and validation of PKRS1 as a novel biological target is therefore an important and exciting development. Representatives from the team at DDU and MMV tell us more.

Figure 2: A co-crystal structure of the early lead compound with lysyl-tRNA synthetase

[The technique]... allows scientists to use 3D computational models to visualize how specific compounds interact with their biological target.
INTERVIEWS

What is the role of PKRS1 in the malaria parasite? What makes it a good drug target?

DB. PKRS1 is a key enzyme involved in protein synthesis. Without it, the parasite cannot grow and therefore cannot survive. Unusually, PKRS1 is present across all stages of the parasite lifecycle – both asexual and sexual blood stages, as well as the liver stage – making it an attractive biological target that can address multiple target candidate profiles. PKRS1 is also present in other pathogens, such as the parasite that causes cryptosporidiosis. Compounds active against PKRS1 therefore have the potential to treat not only malaria, but also other neglected tropical diseases.

How was PKRS1 discovered and validated?

DB. The discovery and validation of PKRS1 speaks to the power of collaboration in malaria research. The first step was the discovery of a natural product (cladosporin) active against the malaria parasite, and the subsequent identification of its target (PKRS1) by Prof. Elizabeth Winzeler, one of MMV’s long-term collaborators at the University of California San Diego. Cladosporin was not developable as a drug candidate; however, working through the Structure-guided Drug Discovery Coalition, funded by the Bill & Melinda Gates Foundation, we carried out a project with the specific aim of exploring the potential of PKRS1 as a novel therapeutic target.

Working in collaboration with Prof. Wes van Voorhis at the University of Washington, we identified an inhibitor from a compound screen against PKRS1. This led to the screening of further compound libraries, generating more chemical series for optimization at DDU. We were also able to validate PKRS1 as a drug target in the SCID model of malaria – the first time an animal model has been used to validate this target in the malaria parasite.

Structure-based drug design was also used in this project. Why was this important?

PW. Traditionally, the malaria drug discovery community has relied primarily on phenotypic screening to identify new compounds, but since this approach lacks an understanding of how the compound works in humans, it can make the optimization of a series to deliver a drug candidate more challenging. Structure-based drug design is a more sophisticated (though less commonly used) technique that allows scientists to use 3D computational models to visualize how specific compounds interact with their biological target (Figure 2). On this project, the insights gained from structure-based drug design have enabled us to optimize the potency and selectivity of compounds active against PKRS1.

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

KR. The team synergy has been fantastic. MMV and DDU have enjoyed a successful working relationship for almost 10 years now, starting in 2010/11 with a project that ultimately led to the delivery of a new drug candidate – currently in Phase I testing (M5717 – p. 18). MMV has an in-depth understanding of malaria and an extensive network of global collaborators, which really helps to move compounds along the discovery pathway. At all stages, DDU has benefited enormously from MMV’s advice and mentorship.

DB. Team collaboration has played a fundamental role in the success of this project. Testing new compound series is a logistically complex process as the validated assays for studying different stages of the parasite lifecycle are based all over the world. Without the strong partnerships we have with a wide range of centres – such as Imperial College (London, UK) and TropIQ (the Netherlands) for transmission-blocking assays; DDU (Dundee, UK) and GSK (Tres Cantos, Spain) for asexual blood-stage testing; and centres in Cambodia, Thailand and the USA for liver-stage testing – this work would simply not be possible.

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

BB. It’s a great endorsement for the team. The drug discovery pathway is a long one, and we first started working on this project back in 2014. This award recognizes the consistently hard work of the project team and its collaborators, and also motivates us to keep pushing forward. We are particularly proud given the many other competitive drug discovery projects currently active in MMV’s portfolio.

What are the next steps for this project?

DB. Our focus now is on improving the properties of the compound series to deliver a drug candidate that can pass all the safety milestones required to advance to clinical development. Because PKRS1 is an enzyme essential for protein synthesis, we know that if we can successfully develop a drug candidate, it could kill the parasite at several different stages in the lifecycle, giving rise to a compound with good therapeutic potential for malaria. Going forward, we will continue to ensure that the goals of the project align with MMV’s target candidate profiles and strategic imperatives, as well as the global elimination and eradication agenda for malaria.

Dr Beatriz Baragaña
Drug Discovery Unit (DDU), University of Dundee, UK

Prof. Ian Gilbert
DDU, University of Dundee, UK

Paul Willis
Senior Director, Drug Discovery, MMV

Prof. Kevin Read
DDU, University of Dundee, UK

Delphine Baud
Project Coordinator, Drug Discovery, MMV

Paul Willis
Senior Director, Drug Discovery, MMV

Prof. Kevin Read
DDU, University of Dundee, UK

Delphine Baud
Project Coordinator, Drug Discovery, MMV
Improving case management of uncomplicated malaria

Increasing treatment options for children with uncomplicated malaria

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

MMV and partners have prioritized the discovery, development and delivery of new and effective antimalarial drugs for children. In February 2009, MMV and Novartis launched Coartem® Dispersible (artemether-lumefantrine), the first ever high-quality artemisinin-based combination therapy (ACT) developed especially for children. As of year-end 2018, 385 million treatment courses had been provided to vulnerable children suffering from malaria – a volume that MMV estimates to have saved around 825,000 lives.¹

The second child-friendly ACT to emerge from MMV’s pipeline was a granule formulation of Pyramax® (pyronaridine–artesunate),² which was granted a positive scientific opinion by the European Medicines Agency (EMA) in 2015.³ Co-developed by MMV and Shin Poong Pharmaceutical, Pyramax granules are now included on the World Health Organization (WHO)’s List of Prequalified Medicinal Products¹ and Essential Medicines List (EML)⁵ for children (EMLc).

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

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

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

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

Expanding access to ACTs with real-world studies

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

One such study is the Phase IIIb/IV CANTAM² study, which is gathering data on the use of Pyramax in treating 8,572 malaria episodes in adults and children across five endemic countries in sub-Saharan Africa. It is hoped that data from this study will support the roll-out of Pyramax in a wider range of patients, including those with co-infections and abnormal liver function, as well as in very young children (<1 year of age), and children who are malnourished. Completion of enrolment is expected in the first quarter of 2019.

Another novel post-approval study involving Pyramax is underway in Zambia and The Gambia. This study is exploring the efficacy of different dosing regimens of Pyramax in clearing parasites in individuals who are infected with Plasmodium falciparum, but are asymptomatic (i.e. show no clinical symptoms of the disease yet remain an important reservoir for transmission). Enrolment is expected to be complete in the first quarter of 2019. Positive results from this study may inform future approaches for community-wide treatment campaigns in which asymptomatic carriers represent a large portion of the target treatment group.⁶
3. Improving case management of uncomplicated malaria

Developing next-generation cures

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

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

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

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

### Notes

9. Resistance to artemisinin can in turn lead to resistance to the partner drug.

10. A prophylactic drug kills the liver-stage (sporozoite) form of the malaria parasite, thereby halting the parasite lifecycle and preventing a subsequent blood-stage infection from taking hold.
Artefenomel (OZ439)/ferroquine (FQ)

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

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

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

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

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

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

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

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

Why is ganaplacide/lumefantrine an exciting combination?

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

How is the Phase IIb trial progressing?

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

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

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

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

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

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

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

The compound offers the dual possibility of becoming part of a SERC or a next-generation treatment for severe malaria.

Cipargamin (KAE609)

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

The sodium channel in the parasite targeted by cipargamin (PfATP4) is the first validated new molecular target for malaria in more than 20 years. In a Phase IIa proof-of-concept study in Thailand, cipargamin rapidly cleared parasites from the blood of adults with uncomplicated P. falciparum or P. vivax malaria.14 A subsequent study showed the compound’s good longevity in the blood, with a 75 mg dose staying above the concentration needed to kill parasites for over 8 days. In addition to its asexual blood-stage activity, cipargamin has shown the potential to block transmission of malaria.15

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

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

Novartis is developing cipargamin in collaboration with MMV with financial and technical support from Wellcome Trust.16

---

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

---

Improving case management of uncomplicated malaria
3. Improving case management of uncomplicated malaria

Maintaining a healthy pipeline of candidate antimalarial drugs

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

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

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

M5717

M5717 (formerly DDD498), in development with Merck KGaA, is the first compound in the portfolio to have shown comparable activity across all stages of the parasite lifecycle (except for the dormant liver stage of *P. vivax* malaria), as well as prophylactic activity.

In 2018, single, ascending doses of M5717 were evaluated in a Phase I study, and the compound was shown to be safe and well tolerated. The challenge now is to find the ideal combination partner. Using the SCID model, M5717 has been studied in combination with several of MMV’s priority compounds, with several other combination studies initiated. After completion of the Phase I study, the next stage will be to select the best combination partner and to start combination studies in humans.

MMV253

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

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

18 SCID model: the laboratory model of malaria that provides the most accurate prediction of drug response in humans.
19 Conducted in line with international good laboratory practice (GLP) and good manufacturing practice (GMP) guidelines.

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

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

New drug candidates

In 2018, MMV’s Expert Scientific Advisory Committee20 recommended three new candidates for progression to preclinical testing: a new endoperoxide, MMV052;21 a novel compound from GSK, GSK701;22 and two prodrugs23 of atovaquone for use in a potential injectable prophylactic drug (MMV370/MMV371; with a view to selecting one during preclinical safety studies). In 2018, MMV and Sanofi successfully completed preclinical safety and toxicology studies, and the compound has now been approved by MMV’s Global Safety Board for testing in human volunteers.

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

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

In 2017, an estimated 435,000 people lost their lives to malaria. The overwhelming majority of these deaths (93%) occurred in Africa, mostly in children aged under 5 years (61%). Severe malaria is one of the biggest killers of young children. The condition can develop from uncomplicated malaria within a matter of hours, with symptoms including, but not limited to anaemia, hypoglycaemia, respiratory distress, convulsions and coma.

The World Health Organization (WHO) recommends injectable artesunate (Inj AS), in preference to quinine or artemether, for the treatment of severe malaria – due to its superior efficacy. The WHO also recommends rectal artesunate (RAS) for “pre-referral treatment of severe malaria in children under 6 years of age in remote areas […] pending immediate transfer to a higher-level facility where comprehensive care can be given.”

MMV and its partners are working to improve access to quality-assured versions of these medicines and help improve overall case management of severe malaria.

Injectable artesunate: improving outcomes for children and pregnant women

Since WHO prequalification (WHO-PQ) of Artesun®, Fosun Pharma’s Inj AS product, in 2010, more than 128 million vials have been dispatched worldwide, sufficient to treat an estimated 21 million children. Given that Inj AS offers a 22–35% reduction in mortality compared to the alternative treatment for severe malaria, quinine, it is estimated that more than 840,000 additional lives have been saved by Inj AS since its launch, compared with the number that would have been saved by quinine.

As the first WHO-prequalified Inj AS treatment on the market, Artesun is now in widespread use – approved in 35 countries worldwide.

To ensure a sustainable global supply of quality-assured Inj AS, MMV is supporting additional manufacturers in their efforts to achieve WHO-PQ. In December 2018, Ipca Laboratories achieved prequalification of its Inj AS product Larinate®. In 2019, MMV will continue to support the introduction and scale-up of both quality-assured Inj AS products, collaborating with malaria-endemic countries and stakeholders to support improved severe malaria case management. In addition, MMV is working with manufacturers to simplify the administration of Inj AS by reducing the number of vials required.

MMV has also worked closely with public health partners to develop training materials for healthcare workers on Inj AS (now available in four languages), aimed at giving clear and easy-to-understand information on product dosing. Nearly two dozen countries have adopted these materials, incorporating them into their national training programmes. MMV consistently seeks feedback on its training materials to make sure that healthcare workers have the information they need to deliver the right standard of care.

Management of severe malaria in pregnant women is an additional challenge. To improve outcomes for this vulnerable group, MMV is collaborating with countries to align with WHO guidelines for the management of severe malaria during pregnancy. By mapping out the capacity gaps in endemic-country healthcare systems, MMV is working with National Malaria Control Programmes (NMCPS) in five countries to develop a plan for improving severe malaria case management in pregnant women.
Rectal artesunate: buying time to save lives

In 2005, the WHO recommended the use of RAS for the pre-referral management of severe malaria in young children, and in 2017, RAS (100 mg) was added to the WHO Essential Medicines List and Essential Medicines List for Children.9 Despite these guidelines, no WHO-prequalified, quality-assured RAS product was, until very recently, available – severely limiting its use and denying millions of children access to its benefits.

Supported by Unitaid grants, MMV has worked closely with two partners, Cipla Ltd and Strides Pharma Science Ltd, over the past 5 years, to bring to market quality-assured RAS (100 mg) products.10 In February 2018, Cipla’s product achieved WHO-PQ and is now approved for use in seven malaria-endemic countries in Africa. In June 2018, the Strides product also achieved WHO-PQ and is now approved in eleven countries. RAS has been enthusiastically welcomed by African countries: in Zambia, for example, the National Malaria Elimination Centre (NMEC) and Ministry of Health have already agreed to scale up RAS at the community level, with the aim of making it available nationwide.

WHO-PQ of the Cipla and Strides products has accelerated procurement of RAS in endemic countries, with the latest data showing an upward trend in its use. In 2018, an estimated 1.7 million RAS products were ordered by endemic countries – a substantial increase compared with 2017, and of those orders, 1.5 million were for WHO-prequalified quality-assured RAS 100 mg.11 As such, over 85% of RAS procured in 2018 by the three largest international buyers – The Global Fund, President’s Malaria Initiative and UNICEF – was quality-assured.

With funding from Unitaid, MMV is working to support improved introduction and scale-up of RAS. This work is further supported by the community access to rectal artesunate for malaria (CARAMAL) project, led by the Clinton Health Access Initiative. The project is focused on three high-burden countries – Democratic Republic of the Congo, Nigeria and Uganda – and is currently piloting community case-management schemes and multi-country observational research to identify the operational and health system-related factors affecting the introduction of RAS.

Severe Malaria Observatory: sharing best practice

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 gives stakeholders a chance to share knowledge, experience and treatment guidance relating to severe malaria (the site houses numerous reports and surveys), thereby deepening global understanding of, and expertise in, the disease.

Specifically, the SMO 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 January 2019, the SMO was, on average, receiving more than 5,000 hits per month, with the majority of visits coming from African stakeholders. In just 1 year since the SMO was launched, the number of site visits has increased five-fold, demonstrating the value of this resource for the global community.

www.severemalaria.org

---

9 The WHO followed this up with an ‘information note’ in October 2017, describing when, and how, to administer the treatment.
10 Building on work initiated by the WHO’s Special Programme for Research and Training in Tropical Diseases (TDR), not funded by Unitaid.
11 Instead of alternative, non-WHO-approved 50 mg and 200 mg formulations.
4. Accelerating access to severe malaria interventions

MAM initiative: increasing access to rectal artesunate in rural communities

In July 2017, MMV joined forces with an international development organization, Transaid, as well as Development Data, DAI Global Health, Disacare and the NMEC of Zambia, to implement a pilot access project that reduced malaria case fatality by a dramatic 96%.

The project, known as MAMaZ Against Malaria (MAM), introduced the use of RAS at the community level, and used locally operated bicycle ambulances to improve the transport of sick children to health centres, as well as community theatre, song and dance to raise awareness of malaria danger signs. The project was conducted in the Serenje district of Zambia’s central province, and reached 54,000 people across 45 communities, served by a total of eight health facilities.

In every suspected case of severe malaria, children were given quality-assured 100 mg RAS (by one of 447 trained community health volunteers – CHVs) before being transferred to a health facility, where they received Inj AS followed by a 3-day oral course of artemisinin-based combination therapy (ACT). The project’s bicycle-based emergency transport system (ETS) was involved in more than 70% of these cases, making a total of 1,066 health facility transfers.

Over the 12-month pilot period (August 2017 to July 2018), only three deaths (0.25%) were recorded for 1,215 cases of severe malaria, compared with 97 deaths (8%) that would otherwise have been expected to occur in this timeframe. This represents a dramatic overall reduction in the case fatality rate of 96%.

The success of the MAM pilot provides undeniable evidence that through targeted interventions (e.g., providing RAS and ETS in tandem), it is possible to save the lives of vulnerable children with severe malaria – even in access-challenged rural settings.

MMV has now secured matched funding from Grand Challenges Canada (a non-profit organization) and the Government of Canada to expand the MAM initiative in Zambia from one to two districts, followed by a further three-district expansion, enabling the project to reach four times as many people. Further funding will need to be sought to enable the project to reach all vulnerable children in Zambia.

Zambia has set itself the ambitious goal to eliminate malaria by 2021. How did this goal come about and how will it be achieved?

Despite our best efforts, Zambia continues to experience spikes of malaria. Because of this, we have decided that control is no longer enough – we need to eliminate malaria for good. So, between 2017 and 2021, we are implementing a new strategic plan designed to eliminate local transmission of malaria and, critically, prevent re-introduction of the disease. One important aspect of this is ensuring prompt and effective case management of malaria to reduce the pool of individuals who can contribute to malaria transmission.

What is Zambia’s approach to the case management of severe malaria?

We have revised our national policy to align it with WHO recommendations, that is, replacing quinine with more effective treatments, such as Inj AS. And, having trained up CHVs through the MAM initiative, we can now proactively diagnose and manage cases of severe malaria – using RAS – at the community, pre-referral level, rather than waiting for cases to present at district health facilities.

How can the MAM project be scaled up to close the coverage gaps?

The pilot initiative focused on one district only (Serenje). In the next phase of the project, we will expand into one new implementation district in Central Province (Chitambo) and three national scale-up districts, before scaling up even further. Training is a key part of this expansion. So far, we have trained up to 7,500 CHVs, and we aim to have trained a further 7,500 by the end of 2019. Ultimately, for maximum coverage, we hope that initiatives similar to MAM will one day be present in all 114 districts of Zambia.

How have you benefited from working with MMV and Transaid?

By working with multiple partners, our approach to the management of severe malaria has been comprehensive and well-integrated. Supported by MMV, we were able to introduce and increase access to quality-assured RAS and, supported by Transaid, we were able to scale up and strengthen existing services, such as the bicycle ambulances. Almost 100% of the children treated for suspected severe malaria in the pilot reached a health facility in good time – all thanks to this team approach. I hope that our experience in Zambia will inspire other African countries to consider similar projects and forge new collaborations.
One night in May 2018, 3-year-old Mervis from Kebumba, Serenje District, Zambia, began to show signs of being unwell. She had a high fever and had lost her appetite. By the next morning, the situation had taken a dramatic turn for the worse; little Mervis had begun convulsing.

Priscilla Chibuye, Mervis’ mother, rushed her to the nearest community health volunteer, Idess. Thanks to the training Idess had received through the MAM project, she quickly suspected severe malaria and administered two artesunate suppositories. These helped to stabilize Mervis until she could get to a health facility.

Meanwhile, Justina, an ETS bicycle rider, was called. The journey to Mulilima Rural Health Centre took an hour and a half. On arrival, it was confirmed that Mervis was suffering from severe malaria.

She was promptly given Inj AS. Later that evening, following her second dose of treatment, Mervis was already starting to show signs of improvement. She began to show interest in her surroundings and ask for food again. The next morning, Mervis received her third and final dose of Inj AS and was soon discharged. Mum Priscilla was given further oral medication to complete Mervis’ malaria treatment at home.

During a follow-up visit Idess made to the family, Priscilla remarked that, before the MAM project came to her community, many children used to die from severe malaria. She was grateful the situation today had changed, and that her own daughter had made a full recovery.
Next-generation tools to tackle relapses

Historically, global efforts to tackle malaria have focused primarily on Plasmodium falciparum malaria, due to its higher disease burden and associated health risks, including death – particularly among children. Conversely, Plasmodium vivax malaria is often neglected, despite having the widest geographical distribution of the five species of parasite affecting humans.

P. vivax accounts for around half of the malaria cases outside sub-Saharan Africa and is often the predominant species of malaria in countries that are close to eliminating the disease. It threatens around 2.5 billion people and causes around 7.5 million clinical infections every year; many of which are relapses of existing infections that occur in the absence of new infective mosquito bites. This occurs because P. vivax parasites can lie dormant in the liver in a form known as hypnozoites, which can reactivate weeks, months or even years after the initial infection.

Until recently, primaquine (PQ) was the only available treatment for the prevention of P. vivax relapses. However, patients often do not comply with the WHO-recommended 14-day treatment regimen for PQ, leading to reduced efficacy. A more compact-dosing regimen to improve compliance was therefore urgently needed.

Tafenoquine: transforming the treatment of relapsing Plasmodium vivax malaria

In July 2018, MMV and its partner GSK celebrated a major milestone: tafenoquine (TQ), a single-dose medicine, became the first new treatment to prevent relapses of P. vivax malaria since the approval of PQ in 1952. TQ was approved (as Krintafel®) by the US Food and Drug Administration for “the radical cure (prevention of relapse) of P. vivax malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute P. vivax blood-stage infection.” In September 2018, a second stringent regulatory authority, the Australian Therapeutic Goods Administration, also approved TQ (as Kozenis®) for the same indication, paves the way for regulatory submissions and review in malaria-endemic countries.

Both PQ and TQ belong to the same class of compounds (the 8-aminoquinolines). Because the 8-aminoquinolines can cause haemolysis in individuals who are deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD), PQ and TQ are contraindicated in this patient population. To help identify patients who are eligible for treatment, MMV and GSK's partner PATH, a non-profit global health organization based in Seattle, has supported the development of a quantitative point-of-care G6PD diagnostic tool – now approved in many countries, including Brazil, Thailand, Myanmar, Indonesia and India.

In 2018, regulatory filings for TQ occurred in Brazil, Colombia and India, with additional filings planned for 2019 in seven other countries across South America, South East Asia and the Horn of Africa. The focus is now on generating evidence to support the adoption of TQ and G6PD in national treatment guidelines, a precondition for ensuring patient access to these tools. Studies to assess the feasibility of providing appropriate radical cure (TQ or PQ) after quantitative G6PD testing, at different levels of the health services, are planned in Brazil, Thailand and Ethiopia. These studies, designed in close collaboration with the respective National Malaria Control Programmes (NMCPs), national experts and the WHO, should provide insight into how best to incorporate the new tools into the case management of P. vivax malaria.

MMV and PATH are engaging with Ministries of Health, NMCPs and key stakeholders in malaria-endemic countries to support national efforts to control and eliminate P. vivax. This work is supported in part by VivAccess, an initiative funded by the Bill & Melinda Gates Foundation, which aims to catalyse the adoption of TQ and new tools for the case management of P. vivax, including a more sensitive point-of-care diagnostic – currently under development. These tools have the potential to deliver both individual and public health benefits in terms of reduced relapses and onward transmission of P. vivax, contributing to its eventual elimination.
Sri Lanka has successfully eliminated malaria. To what would you attribute this success?

Several factors, I would say. A key element was the leadership of the central anti-malaria campaign, which was complemented by a very effective team of regional malaria officers. Before and throughout the elimination phase, the country made sure that sound policies, effective implementation and coordination measures, as well as quality products and services, were in place to maximize the chance of success.

A rigorous monitoring and evaluation approach was also applied to the management of grants. Sri Lanka received grants from The Global Fund for its malaria elimination efforts, and I believe it was the ability to direct these funds where needed that made the difference, probably as much as the actual funding itself.

In South East Asia, *P. vivax* accounts for an increasing proportion of malaria cases. What do you see as the key challenges to the control and elimination of *P. vivax*?

One key challenge is preventing relapses. The current anti-relapse medication is PQ, a 14-day treatment course that can only be given after testing for G6PD activity because the drug can induce acute, life-threatening haemolysis in people deficient in this enzyme. In an ideal world, the G6PD status of every individual would be available as part of routine clinical testing. However, until that becomes a reality, we need a reliable quantitative test for G6PD activity that can be used at the point of care in areas where G6PD deficiency is prevalent. Unfortunately, such testing is not yet available.

Another important challenge is correctly diagnosing *P. vivax*, particularly in settings where microscopy is not readily available. To enable earlier diagnosis and treatment, rapid diagnostic tests for *P. vivax* that are at least as sensitive as those for *P. falciparum* are urgently needed.

The final challenge is blocking transmission. In parts of Asia where malaria persists today, transmission occurs in and near forests, where mosquitoes bite and stay outdoors. As such, they are not very amenable to house-spraying with insecticides or to the use of insecticide-treated bed nets, making it very difficult to control the vector.

Despite these challenges, several countries have either already eliminated, or are moving towards, eliminating *P. vivax* malaria, which shows that the tools we already have at our disposal can in fact not only control, but eliminate, the disease.

Do you think that the new tools could revitalize efforts to control *P. vivax* malaria?

Yes, I do. If we could achieve radical cure in every patient with *P. vivax*, it would have a huge impact on transmission. This is because relapses, which account for a large proportion of infections, contribute substantially to the human reservoir of infectious parasites. TQ is a newly approved single-dose radical cure that, in combination with G6PD testing, could help to deplete this reservoir. The challenge is translating this efficacious combination of interventions into a workable practical approach.

Safety is probably the single most important consideration with TQ. Even with a highly accurate test for G6PD activity, the safety of TQ depends on our ability to use it correctly. It is difficult to predict how (whether) and at what level of the healthcare system we can entrust healthworkers to use the test reliably, and to what extent countries will actually adopt and use the system. Any actual, or even perceived, adverse event related to improper use or interpretation of the G6PD test could seriously jeopardize its uptake.

What needs to be done to support the use of a G6PD quantitative test plus TQ or PQ within malaria control programmes?

The only way of knowing if the use of G6PD testing plus TQ or PQ is well tolerated and effective in practice is to carry out feasibility studies in a range of endemic countries that already have safety precautions in place. These experiences could then inform decisions about where in the health system these tools could be safely introduced.
Assays and anti-relapse series

With single-dose TQ now approved for the treatment of relapsing *P. vivax* malaria, it is hoped that endemic countries will soon be able to make further inroads towards elimination of the disease. However, both TQ and PQ are associated with haemolysis in patients with severe G6PD deficiency, and this means they cannot be used in pregnant women, since the G6PD status of the foetus is unknown. As such, new treatments for relapse prevention, suitable for use in all patients regardless of G6PD status, are urgently needed to support these continued efforts.

Identifying compounds active against *P. vivax* hypnozoites has proved challenging, since the parasites are difficult to access and maintain in laboratory assays. However, thanks to the efforts of the Bill & Melinda Gates Foundation liver-stage consortium and MMV’s drug discovery partners, new assays to screen compounds against the liver stages of *P. vivax* malaria (including hypnozoites) are now up and running in Thailand, Cambodia and the USA, and are currently under development in India and Brazil.

In 2016, Dr Jetsumon Sattabongkot Prachumsri and her team, based at Mahidol University, Thailand, became the first research group to test 30 MMV portfolio compounds in an *in vitro* assay of *P. vivax* parasites, enabling MMV to prioritize a chemical series for which only rodent liver-stage activity was otherwise known. Data from Dr Prachumsri’s assay have helped to confirm the liver-stage activity of several of MMV’s translational compounds.

A separate research group, led by Prof. Dennis Kyle at the University of Georgia, USA, has developed a higher-throughput *P. vivax* liver-stage assay that uses human primary liver cells. Using sporozoites supplied by partners in Thailand and Cambodia, the team has now, for the first time in the history of *P. vivax* research, been able to screen two small-scale libraries of chemical entities, representing around 30,000 data points. Several potential radical cure molecules have been identified and chemical optimization is underway with a view to launching a full drug discovery programme. If all progresses as expected, this could potentially lead to a new clinical candidate for relapsing *P. vivax* malaria entering the malaria drug pipeline within the next 4 years. In 2019, MMV and its partners at the University of Georgia expect to deliver an additional 60,000 data points with the hope of identifying new chemical series with anti-relapse potential.

…the team has now, for the first time in the history of *P. vivax* research, been able to screen... around 30,000 data points.
Protecting the most vulnerable

Despite the intensive efforts of the global malaria research community, the challenges of developing a malaria vaccine with at least 75% protective efficacy\(^1\) have yet to be overcome. In the absence of such a vaccine, the WHO recommends seasonal malaria chemoprevention (SMC) for young children\(^2\) and intermittent preventive treatment (IPTp) for pregnant women. MMV and its partners are working hard to maximize access to currently available quality-assured preventive antimalarials while seeking new alternatives for these vulnerable groups.

### Seasonal malaria chemoprevention

In 2012, the WHO recommended SMC to protect children aged 3 months to 5 years in areas of seasonal malaria transmission in the Sahel region of sub-Saharan Africa. The medicine used for SMC, sulfadoxine-pyrimethamine plus amodiaquine (SPAQ), is administered once a month throughout the rainy season, and in clinical trials has demonstrated a 75% reduction in the incidence of all malaria.\(^3\)

In 2018, 81 million monthly courses of SPAQ treatment were shipped during the SMC season – estimated to have provided protection for more than 20 million children and bringing the total number of treatment courses distributed since its launch in 2014\(^4\) to 250 million.

Only one WHO-prequalified SPAQ product is currently available. To increase the number of quality-assured suppliers and thereby help to provide security of supply, MMV is supporting S Kant Healthcare to develop its assured IPTp. So far, this new packaging has been impacted by seasonal malaria, MMV is considering new combinations of existing therapies as alternatives to SPAQ. In addition, MMV is investigating new treatment strategies for long-duration prophylactic treatments (>1 month), including intramuscular formulations of prodrugs\(^9\) and potential new therapies based on monoclonal antibody technology.\(^10\)

### Intermittent preventive treatment in pregnancy

The WHO recommends IPTp using SP for all pregnant women during antenatal visits, starting as early as possible in the second trimester. Despite adoption of this policy in 39 African countries, access to IPTp remains disappointingly low. According to the World Malaria Report 2018, among the 33 countries that provided data in 2017, only ~22% of eligible pregnant women received the three recommended doses of IPTp, clearly showing the extent of the coverage gap.

MMV is working to develop adapted packaging for quality-assured IPTp. So far, this new packaging has been tested in Democratic Republic of the Congo, Nigeria and Mozambique, helping to improve perceptions of SP as a quality medicine for chemoprevention during pregnancy.

Furthermore, for regions where SP resistance is a concern, MMV is working to identify potential substitutes for the drug in IPTp, including supporting work to repurpose existing treatment drugs. In 2014, a study to assess the cardiac safety of Eurartesim\(^\text{®}\) (dihydroartemisinin-piperaquine) in pregnant women began in Tanzania to evaluate its potential as an alternative to SP.\(^7\)
Tenin’s story
Living happily, protected from malaria

Tenin Keita is 3 years old and lives with her family, including her baby brother Moussa, in the Dabola prefecture of the Faranah Region of Guinea. This region is plagued with malaria, especially during and just after the rainy season from July to October. Today, SMC is being rolled out to protect children like Tenin and her brother from malaria, and the results are impressive. Tenin and Moussa’s mother, Fatoumata Binta Diallo, happily explains that none of her children suffered from malaria in 2018.

This wasn’t always the case. The year before there had been many more cases of malaria in the village. “Yes, it’s changed,” explains Fatoumata. “My neighbour’s daughter was really very ill last year. Now she’s ok. She’s been better since we got the medicines. The children don’t cry, it’s fine. They take them without any problem.”

SMC was provided to all eligible children in the Dabola prefecture, Guinea, for the first time in 2018. The director of the Dabola area hospital explained that there had been a 25% reduction in malaria-related hospital admissions between 2017 and 2018 – since the implementation of SMC. As a practical illustration, he also noted there had been an important decrease in the demand for blood bags for transfusion, which he attributed to a decrease in the number of children with severe anaemia caused by malaria.
Identifying optimal drug combinations

Developing new antimalarial medicines that can successfully treat the disease and combat drug resistance requires the use of at least two drugs in combination, each with a different mechanism of action and resistance profile. With 15 compounds currently in preclinical and early translational development, understanding how different candidate compounds interact in order to select the best combinations for clinical development is a highly complex process.

Human volunteer infection studies and SCID models

To accelerate the selection of next-generation drug combinations, MMV and its partners are using two pioneering technologies in the field of translational science and experimental medicine: the SCID mouse model and human volunteer infection studies (VIS).

The SCID model is a laboratory model of human malaria, which allows scientists to predict the activity of candidate compounds and generate data to inform the design of clinical studies in humans. SCID testing in 2018 occurred at the Swiss Tropical and Public Health Institute (Swiss TPH), as well as at two sites in Spain: one in Tres Cantos (GSK) and the other in Bilbao (The Art of Discovery [TAD]).

In 2018, 15 new combinations of MMV compounds were evaluated in SCID models to inform the choice of partner drugs. The SCID model is now also starting to provide insights into how standard antimalarial drugs are affected by resistance. This is achieved by comparing the activity of a given drug in a model with malaria parasites that are sensitive to key antimalarial drugs (the *Plasmodium falciparum* 3D7 strain), versus its activity in a model using artesinin-resistant parasites.

Data from the SCID studies allow MMV to model the pharmacokinetic and pharmacodynamic properties of new drug combinations, which enable the best combinations to be selected for human VIS. The VIS were first developed to assess the blood-stage activity of single candidate compounds, but recent technological developments have allowed researchers to gain insights into the prophylactic and anti-gametocyte activity of candidates, as well as the activity of different compounds in combination and more recently, against resistant strains of parasites (Figure 3).

Humanized FRG model

Until recently, it was only possible to study the complete liver stage (both for anti-relapse and prophylaxis) of parasite development using non-human species of malaria in rodents or primates. However, an exciting new tool, originally developed by Prof. Stefan Kappe and his team at the Center for Infectious Disease research in Seattle (and which now is being established at TAD, in collaboration with TropIQ and MMV), has changed what is possible. The FRG mouse model, makes it possible to study how the malaria parasites that infect humans develop first in the liver and then enter the blood to cause a clinical infection. In short, the model allows researchers to mimic more of the human parasite lifecycle than ever before – all in a non-human host.

As is being shown by the Kappe lab and others, the FRG model could prove particularly useful in the study of *P. vivax* malaria, shedding light on its complex liver stage of development. For the first time, assuming access to *Plasmodium vivax* sporozoites, it will be possible to see whether a given compound can kill hypnozoites in vivo in a rodent model. As such, the data obtained from the model will be more physiologically relevant than data from in vitro studies, generating important insights about a compound before human testing. The FRG model is currently being established and validated for *P. falciparum* malaria, and the first full study on a new compound will be run in 2019.
The volunteer infection study platform is a valuable tool for accelerating the evaluation of promising new drugs. In a tightly controlled environment, volunteers receive a low number of drug-sensitive or drug-resistant malaria parasites (sporozoites) and the level of parasitaemia in their blood is monitored closely. Around 7 days later, the volunteers receive the experimental drug candidate, while parasitaemia continues to be monitored. In this way, these studies enable us to understand quickly whether a compound will be efficacious against malaria and/or known resistant strains of malaria and guide dose selection for subsequent clinical studies.

In the same study, we can also explore the activity of experimental drugs against the sexual (gametocyte) stages of the malaria parasite to assess transmission-blocking activity. The simplest way is to monitor the development of gametocytes at the same time as blood-stage parasitaemia. In addition, we can feed mosquitoes with the test subject’s blood containing gametocytes to see if the drug can prevent transmission.
Evolution of drug discovery

How have MMV’s discovery activities evolved over the past year?

In 2018, we continued to focus our discovery efforts on delivering a steady stream of new preclinical candidates. However, through the use of novel platforms – such as Plasmodium liver and gametocyte in vitro assays, in vivo SCID and FRG models, and the human VIS – we are now developing a much deeper understanding of the potential of new series and targets. This has allowed us to identify new compound series active beyond the blood stage of the parasite lifecycle and optimize them for clinical development. As such, the range of profiles displayed by preclinical candidates is evolving.

Can you tell us about new screening collaborations?

MMV is a founder member of MaLDA – the malaria drug accelerator, a network of academic and industry labs funded by the Bill & Melinda Gates Foundation, and led by Prof. Elizabeth Winzeler at University of California, San Diego. Through research involving resistance selection, genomic analysis and editing, metabolomics, proteomics, conditional gene knockdowns and full malaria lifecycle fingerprinting, MaLDA is helping us to identify new drug targets and mechanisms of action for confirmed antimalarial compounds identified from screening. In 2018, we worked very closely with MaLDA, supplying compounds, prioritizing biological targets and discussing key MMV portfolio projects. Ultimately, we hope that collaborations with MaLDA and MMV’s partners will bring about a renaissance in target-based drug discovery. This would be significant, as knowing what the biological targets are gives us a real advantage for compound optimization, as per MMV’s Project of the Year 2018 (pp. 10–11).

What are the key lessons learned from 2018?

We continue to learn from the successes and failures of different projects. As more and more candidates are delivered, we develop a greater understanding of the potential risks and liabilities of different compound series. One recent example is SJ733, a compound that in 2018 was found to have lower concentrations in humans than expected. Although no longer in MMV’s portfolio, our experience with SJ733 has informed the development of a back-up series by a project team led by Prof. Kip Guy at the University of Kentucky, which, crucially, aims to circumvent the liability identified in SJ733. As such, the “failure” of SJ733, viewed from a different perspective, will hopefully catalyse the success of a back-up.

“Ultimately, we hope that collaborations with MaLDA and MMV’s partners will bring about a renaissance in target-based drug discovery.”
MMV Open: stimulating research into neglected and pandemic diseases

Since the turn of the 21st century, the world has battled multiple epidemics – both old and new, viral and bacterial. Some of these have reached pandemic proportions. The Zika virus outbreak across the Americas in 2015–2016, for example, demonstrated how quickly a relatively unknown mosquito-borne disease can become a global health emergency.

Drug-resistant pathogens have the potential to increase the frequency and gravity of pandemics, posing a major threat to the world’s population. Alarmingly, current estimates suggest that the number of deaths associated with antimicrobial drug resistance could increase to 10 million per year by 2050.8

New and innovative approaches to drug discovery are needed to foster new research into treatments for neglected and potentially pandemic diseases. One such approach – “open innovation” – has the power to do just this. Since 2015, MMV has pioneered several drug discovery initiatives to support R&D efforts in malaria and other disease areas – all under the ethos of open innovation.

The first open-source library made available by MMV was the Malaria Box, a collection of 400 diverse compounds with antimalarial activity, distributed free of charge to 30 countries between 2011 and 2015. Over this period, more than 250 boxes were provided to research groups around the world, resulting in 56 publications. In 2015, a second library, the Pathogen Box, was made available. Containing 400 diverse, drug-like molecules active against neglected tropical diseases of interest, 319 copies of the Pathogen Box had been shipped to 42 countries, generating 32 publications, by the end of 2018.

The latest open-source library to be made available is the Pandemic Response Box, launched by MMV and the Drugs for Neglected Disease initiative in January 2019.

We spoke to Kirandeep Samby, a medicinal chemist and MMV consultant working on MMV Open activities, to find out more about this latest initiative.

What is the Pandemic Response Box?

The Pandemic Response Box is a new library of 400 diverse compounds with antibacterial, antiviral or antifungal activity. It is freely available to members of the scientific community upon request. In return, researchers are required to publish any findings in an open-access journal within 2 years of data generation.

What types of compounds are included? How were these selected?

Anti-infective compounds included in the box are in various phases of discovery or development. Initially, we took around 20,000 compounds that were reported in the public domain and had relevant biological activity. These were triaged using computational techniques to provide a selection of compounds with a range of molecular properties, chemical scaffolds, target pathogens and biological mechanisms of action. Around 2,300 compounds were then shortlisted from this triage. Lastly, a group of external disease experts assessed each of the 2,300 compounds individually and selected the final set of 201 antibacterial, 153 antiviral and 46 antifungal compounds.

What is the value of open-source libraries such as the Pandemic Response Box?

In the field of neglected tropical diseases, initiatives like the Pandemic Response Box are vital. Such libraries give scientists the tools to explore and validate new targets, which in turn leads to new scientific discoveries and new drug discovery projects. The overarching goal of the project is to help shorten the time between a new pandemic emerging and new drugs becoming available to treat it, because as we know from experience, saving time saves lives.

How many orders do you expect to receive?

Based on our experience with the Malaria Box and Pathogen Box to date, we expect to receive orders for around 200–300 boxes. However, it will probably take 2–3 years to reach this number.

What has it been like working with MMV?

It’s been a wonderful experience. MMV is a very open organization to work with and is always receptive to feedback from its partners. I believe the work they do is extremely important in safeguarding our society from future threats to global health.

InterVIEW

Kirandeep Samby
Medicinal Chemist,
MMV Consultant, India,
talks about MMV’s latest open access initiative.
2018 has been a successful year for MMV in many respects.

Total revenues reached a level of 97.2 million United States dollars (USD), largely thanks to the continued commitment of our donors (in total USD 64.9 million), partly owing to MMV’s contractual share of the Priority Review Voucher (PRV) received by our pharmaceutical partner GlaxoSmithKline (GSK) upon approval of Krintafel (tafenoquine) from the US Food and Drug Administration (FDA) in July 2018 (equivalent to USD 28.4 million, payable 50% in 2019, 25% in 2022 and 25% in 2023).

Total expenditure in 2018 reached a level of USD 84.5 million. This represented a 13% increase relative to the previous year (USD 74.3 million in 2017). Meanwhile research & development (R&D) investments amounted to USD 57.6 million (up 7% compared to USD 53.9 million in 2017). Access & product management expenditure increased to USD 14.6 million (up 86% compared to USD 7.8 million in 2017), including USD 4.6 million related to MMV’s investment in the Central Africa Network on Tuberculosis, HIV/AIDS and Malaria (CANTAM) Pyramax® study. In 2018, external relations, board & stakeholders and general & administration expenditure cumulatively accounted for 13.5% of total expenditure, in line with previous years.

In 2018, the Bill & Melinda Gates Foundation renewed its grant to MMV for the 5-year period 1 July 2019 – 30 June 2024, for a total amount of up to USD 180 million – the largest single donation ever pledged to MMV since its foundation in 1999. In 2018, MMV also received new grants from the Australian Department of Foreign Affairs and Trade (DFAT), ExxonMobil and Global Health Innovative Technology Fund (GHIT). MMV is grateful for these and previous commitments from its donors.

In December 2018, Sanofi and MMV agreed that operational responsibility and leadership of the Phase IIb artefenomel/ferroquine drug combination development programme would transfer to MMV. Accordingly, at the end of December 2018 Sanofi executed an indemnity payment of EUR 17,014,000 (equivalent to approximately USD 19.5 million and booked in 2018 as “deferred revenue”) for completion by MMV of the above-mentioned Phase IIb study activities from 1 January 2019 onwards.

Following the above-mentioned extraordinary payment from Sanofi, MMV’s total cash balance as of 31 December 2018, increased to USD 57.4 million. The total capital of the organization increased to USD 63.2 million, of which USD 47.9 million were unrestricted reserves, USD 11.3 million restricted reserves, and USD 4 million paid-in capital. As noted above MMV must, and does, maintain sufficient funds to support the completion of
ongoing clinical studies in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) requirements. Furthermore, long-term financial forecasts indicate that the organization will have to close a significant funding gap to support its 2019–2023 business plan, as indicated in the paragraph below.

**Financial forecasts**

Management estimates that MMV's current portfolio will require an investment of approximately USD 100 million per annum over the 5-year period 2019–2023. With approximately USD 350 million available at the end of 2018 (USD 57 million cash as of 1 January 2019, USD 265 million committed pledges over the period 2019–2023 and the above-mentioned USD 28.4 million receivable from pharmaceutical partner GSK), the organization is currently tracking a shortfall of approximately USD 150 million up to the end of 2023.

Although fundraising activities in 2018 were successful and significant additional funds were sourced, major fundraising efforts will be required in 2019 and beyond, as MMV strives to meet the projected financial requirements of its growing portfolio. MMV has several pending proposals to donors and remains active in its resource mobilization and advocacy activities.

**Legal status**

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. The consolidated financial statements of MMV also include the accounts of the United States entity MMV North America Inc., which is registered in the United States as a section 501(c)(3) organization (please refer to note 2.c of the consolidated financial statements).

**Business model**

MMV receives funding and support from government agencies, private foundations, international organizations, corporations, corporate foundations and private individuals. These funds are used to finance MMV’s portfolio of R&D projects (historically 70–80% of total expenditure), as well as specific, targeted access & product management (APM) interventions that aim to facilitate increased access to malaria medicines by vulnerable populations in disease-endemic countries and support their appropriate use (historically 5–15% of total expenditure).

Since its foundation in 1999, MMV has brought forward ten new antimalarial drugs and taken over the access stewardship of two more. Together, these medicines have saved an estimated 1.9 million lives. With partners, MMV has also established the world’s largest R&D pipeline of innovative, new antimalarial medicines, designed to address remaining unmet medical needs and support the push towards malaria elimination and eradication.

MMV’s private sector partners support joint projects through co-investment and by contributing expertise and facilities. We estimate that for every USD invested, MMV leverages approximately USD 1 in matched funds for external costs, plus USD 1.5 of in-kind contributions through its partners, resulting in a total investment impact of USD 3.5.

**Tax status**

As a not-for-profit Swiss foundation, MMV is exempt from Swiss cantonal and federal taxes and is the equivalent of an exempt organization within the meaning of section 501(c)(3) of the United States Internal Revenue Code. Furthermore, from 1 January 2011, the Swiss Federal Council granted MMV the status of ‘Other International Organization’ conferring certain privileges and immunities including exemption from VAT in Switzerland – representing an estimated additional contribution from Switzerland to MMV of approximately 1 million Swiss francs (CHF) per annum.

**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

---

**Figure 5: MMV expenditure 2018**

Total: USD 84.5 million

- **Research & development**: 69%
- **Access & product management**: 17%
- **General & administration**: 7%
- **External relations**: 6%
- **Foundation board & stakeholders**: 1%

---

**New pledges received in 2018**

<table>
<thead>
<tr>
<th>Donor</th>
<th>Amount in USD</th>
<th>Amount in original currency</th>
<th>Title of grant</th>
<th>Time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bill &amp; Melinda Gates Foundation (BMGF)</td>
<td>180 000 000</td>
<td>USD 180 000 000</td>
<td>New agreement</td>
<td>2019-2024</td>
</tr>
<tr>
<td>Australian Department of Foreign Affairs and Trade (DFAT)</td>
<td>13 193 438</td>
<td>AUD 18 750 000</td>
<td>New agreement</td>
<td>2018-2024</td>
</tr>
<tr>
<td>ExxonMobil Foundation</td>
<td>400 000</td>
<td>USD 400 000</td>
<td>Thematic grant</td>
<td>2018</td>
</tr>
</tbody>
</table>

**TOTAL**                                      | **194 027 441** |
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, investment and cash management facilities in multiple currencies.

Foreign exchange exposure
MMV operates in a multi-currency environment. Cash inflows from donors are largely received in US dollars 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 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 standalone 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 6: MMV income and expenditure to date and scenario 2019-2023
Report on summarized consolidated financial statements to the management of

MMV MEDECINES FOR MALARIA VENTURE, Meyrin

We have audited the financial statements of the MMV MEDECINES FOR MALARIA VENTURE for the year ended 31 December 2018 from which the summarized financial statements were derived, in accordance with Swiss law and Swiss Auditing Standards. In our report dated 5 April 2019, we expressed an unqualified opinion on the financial statements from which the summarized financial statements were derived.

In our opinion, the accompanying summarized financial statements are consistent, in all material respects, with the 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 summarized financial statements should be read in conjunction with the financial statements from which the summarized financial statements were derived and our audit report thereon.

KPMG SA

Hélène Béguin
Licensed Audit Expert
Auditor in Charge

Jerôme Glaus
Licensed Audit Expert

Geneva, 6 June 2019

Enclosure:
- Summarized financial statements
## MMV CONSOLIDATED STATEMENT OF FINANCIAL POSITION

### ASSETS

#### Current assets
- Cash and cash equivalents: USD 57,409,733 (31 Dec 2018) vs. USD 53,064,589 (31 Dec 2017)
- Tax receivable: USD 47,950 (31 Dec 2018) vs. USD 12,699 (31 Dec 2017)
- Prepaids: USD 645,574 (31 Dec 2018) vs. USD 448,004 (31 Dec 2017)
- Prepaid R&D commitments: USD 703,278 (31 Dec 2018) vs. USD 2,363,626 (31 Dec 2017)
- Prepaid APM commitments: USD 248,130 (31 Dec 2018) vs. USD 594,129 (31 Dec 2017)
- Derivative financial instruments: USD 160,495 (31 Dec 2018) vs. USD (160,495) (31 Dec 2017)

#### Total current assets: USD 83,979,019 (31 Dec 2018) vs. USD 60,824,938 (31 Dec 2017)

#### Long-term assets
- Guarantees: USD 215,103 (31 Dec 2018) vs. USD 215,103 (31 Dec 2017)
- Fixed assets, net: USD 175,554 (31 Dec 2018) vs. USD 172,117 (31 Dec 2017)

#### Total long-term assets: USD 14,604,141 (31 Dec 2018) vs. USD 388,931 (31 Dec 2017)

#### TOTAL ASSETS: USD 98,583,160 (31 Dec 2018) vs. USD 61,213,869 (31 Dec 2017)

### LIABILITIES, CAPITAL & RESERVES

#### Current liabilities
- Accrued R&D commitments: USD 10,491,688 (31 Dec 2018) vs. USD 5,192,786 (31 Dec 2017)
- Accrued APM commitments: USD 1,628,954 (31 Dec 2018) vs. USD 1,181,649 (31 Dec 2017)
- Deferred revenue: USD 19,470,549 (31 Dec 2018) vs. USD 215,103 (31 Dec 2017)
- Other creditors: USD 915,426 (31 Dec 2018) vs. USD 1,161,765 (31 Dec 2017)
- Short-term provisions: USD 708,624 (31 Dec 2018) vs. USD 599,954 (31 Dec 2017)

#### Total current liabilities: USD 35,384,874 (31 Dec 2018) vs. USD 10,184,710 (31 Dec 2017)

#### Capital of the organization
- Paid-in capital: USD 4,000,000 (31 Dec 2018) vs. USD 4,000,000 (31 Dec 2017)
- Restricted operating funds: USD 11,265,709 (31 Dec 2018) vs. USD 17,202,032 (31 Dec 2017)
- Unrestricted operating funds: USD 47,932,577 (31 Dec 2018) vs. USD 29,827,127 (31 Dec 2017)

#### Total capital of the organization: USD 63,198,286 (31 Dec 2018) vs. USD 51,029,159 (31 Dec 2017)

#### TOTAL LIABILITIES, CAPITAL & RESERVES: USD 98,583,160 (31 Dec 2018) vs. USD 61,213,869 (31 Dec 2017)

### MMV CONSOLIDATED STATEMENT OF CHANGES IN CAPITAL

<table>
<thead>
<tr>
<th></th>
<th>Balance at 1 January 2017</th>
<th>Internal funds transfers</th>
<th>Gain for the period</th>
<th>Balance at 31 December 2017</th>
<th>Internal funds transfers</th>
<th>Gain/(loss) for the period</th>
<th>Balance at 31 December 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restricted operating funds</td>
<td>15,754,277</td>
<td>930,883</td>
<td>516,872</td>
<td>17,202,032</td>
<td>(938,565)</td>
<td>(4,997,758)</td>
<td>11,265,709</td>
</tr>
<tr>
<td><strong>TOTAL RESTRICTED OPERATING FUNDS</strong></td>
<td><strong>15,754,277</strong></td>
<td><strong>930,883</strong></td>
<td><strong>516,872</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>
</tr>
<tr>
<td>Foundation 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>Unrestricted operating funds</td>
<td>26,620,513</td>
<td>(5,316)</td>
<td>3,211,930</td>
<td>33,827,127</td>
<td>938,565</td>
<td>17,166,885</td>
<td>51,932,577</td>
</tr>
<tr>
<td><strong>TOTAL UNRESTRICTED FUNDS</strong></td>
<td><strong>30,620,513</strong></td>
<td><strong>(5,316)</strong></td>
<td><strong>3,211,930</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>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>46,374,790</td>
<td>925,567</td>
<td>3,728,802</td>
<td>51,029,159</td>
<td></td>
<td>12,169,127</td>
<td>63,198,286</td>
</tr>
</tbody>
</table>
## MMV CONSOLIDATED STATEMENT OF OPERATIONS FOR THE PERIOD ENDED

### REVENUE

<table>
<thead>
<tr>
<th>Notes</th>
<th>31 Dec 2018 USD</th>
<th>31 Dec 2017 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donation revenue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private foundations &amp; individual donors</td>
<td>24 406 097</td>
<td>31 395 805</td>
</tr>
<tr>
<td>UN agencies</td>
<td>1 313 191</td>
<td>967 992</td>
</tr>
<tr>
<td>Government agencies</td>
<td>38 383 732</td>
<td>39 022 973</td>
</tr>
<tr>
<td>Corporate foundations</td>
<td>776 357</td>
<td>789 885</td>
</tr>
<tr>
<td><strong>Total donation revenue</strong></td>
<td><strong>6</strong></td>
<td><strong>64 879 377</strong></td>
</tr>
<tr>
<td>Of which:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total restricted donations</td>
<td>16 706 770</td>
<td>19 232 545</td>
</tr>
<tr>
<td>Total unrestricted donations</td>
<td>48 172 607</td>
<td>52 944 110</td>
</tr>
<tr>
<td>Revenue from partnerships</td>
<td>32 184 473</td>
<td>4 553 610</td>
</tr>
<tr>
<td><strong>Other income</strong></td>
<td><strong>7</strong></td>
<td><strong>32 339 020</strong></td>
</tr>
<tr>
<td><strong>Total other revenue</strong></td>
<td><strong>7</strong></td>
<td><strong>97 218 397</strong></td>
</tr>
<tr>
<td><strong>TOTAL REVENUE</strong></td>
<td><strong>97 218 397</strong></td>
<td><strong>76 810 269</strong></td>
</tr>
</tbody>
</table>

### EXPENDITURE

<table>
<thead>
<tr>
<th>Notes</th>
<th>31 Dec 2018 USD</th>
<th>31 Dec 2017 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research &amp; development expenditure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Project grants</td>
<td>9</td>
<td>43 589 238</td>
</tr>
<tr>
<td>Project-related variable expenditure</td>
<td>9 / 10</td>
<td>13 653 978</td>
</tr>
<tr>
<td>Expert Scientific Advisory Council expenses</td>
<td></td>
<td>404 256</td>
</tr>
<tr>
<td><strong>Total research &amp; development expenditure</strong></td>
<td><strong>57 647 472</strong></td>
<td><strong>53 902 307</strong></td>
</tr>
<tr>
<td><strong>Access &amp; product management expenditure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Project expenditure</td>
<td>9</td>
<td>10 394 355</td>
</tr>
<tr>
<td>Access-related variable expenditure</td>
<td>9 / 10</td>
<td>4 139 796</td>
</tr>
<tr>
<td>Access &amp; Product Management Advisory Committee</td>
<td></td>
<td>48 345</td>
</tr>
<tr>
<td><strong>Total access &amp; product management expenditure</strong></td>
<td><strong>14 582 496</strong></td>
<td><strong>7 849 653</strong></td>
</tr>
<tr>
<td><strong>External relations &amp; advocacy expenditure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERIA-related variable expenditure</td>
<td>10</td>
<td>2 916 640</td>
</tr>
<tr>
<td>Communications</td>
<td></td>
<td>306 064</td>
</tr>
<tr>
<td>Consultants</td>
<td></td>
<td>410 714</td>
</tr>
<tr>
<td>Stakeholders’ meeting</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Technical writing</td>
<td></td>
<td>444 650</td>
</tr>
<tr>
<td>Travel &amp; meetings</td>
<td></td>
<td>248 904</td>
</tr>
<tr>
<td>IT organizational effectiveness</td>
<td></td>
<td>466 458</td>
</tr>
<tr>
<td>Other expenditure</td>
<td></td>
<td>107 118</td>
</tr>
<tr>
<td><strong>Total external relations &amp; advocacy expenditure</strong></td>
<td><strong>4 900 568</strong></td>
<td><strong>3 728 098</strong></td>
</tr>
<tr>
<td><strong>Foundation board expenditure</strong></td>
<td>15</td>
<td>349 639</td>
</tr>
<tr>
<td><strong>General &amp; administration expenditure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staff-related benefits/compensation</td>
<td>10</td>
<td>3 523 978</td>
</tr>
<tr>
<td>Office &amp; occupancy</td>
<td></td>
<td>1 414 202</td>
</tr>
<tr>
<td>Travel expenses</td>
<td></td>
<td>129 649</td>
</tr>
<tr>
<td>Professional &amp; legal fees</td>
<td></td>
<td>232 494</td>
</tr>
<tr>
<td>Training, education &amp; journals</td>
<td></td>
<td>94 420</td>
</tr>
<tr>
<td>IT general expenses &amp; maintenance</td>
<td></td>
<td>278 024</td>
</tr>
<tr>
<td>Depreciation</td>
<td>4</td>
<td>125 933</td>
</tr>
<tr>
<td>Consultants</td>
<td></td>
<td>253 347</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>132 283</td>
</tr>
<tr>
<td><strong>Total general &amp; administration expenditure</strong></td>
<td><strong>6 184 330</strong></td>
<td><strong>5 802 103</strong></td>
</tr>
<tr>
<td><strong>Other expenses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding reimbursements</td>
<td></td>
<td>833 097</td>
</tr>
<tr>
<td><strong>Total expenditure</strong></td>
<td><strong>84 497 602</strong></td>
<td><strong>74 250 502</strong></td>
</tr>
</tbody>
</table>
RESULT FROM OPERATING ACTIVITIES

<table>
<thead>
<tr>
<th></th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial Income</td>
<td>12 720 795</td>
<td>2 559 767</td>
</tr>
<tr>
<td>Financial Expenses</td>
<td>11 270 782</td>
<td>1 446 209</td>
</tr>
<tr>
<td></td>
<td>(822 450)</td>
<td>(277 174)</td>
</tr>
<tr>
<td></td>
<td>(551 668)</td>
<td>1 169 035</td>
</tr>
<tr>
<td>Net financial result</td>
<td>12 169 127</td>
<td>3 728 802</td>
</tr>
</tbody>
</table>

NET SURPLUS PRIOR TO ALLOCATIONS

<table>
<thead>
<tr>
<th>Allocations</th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer (to)/from unrestricted operating funds</td>
<td>(17 166 885)</td>
<td>(3 211 930)</td>
</tr>
<tr>
<td>Transfer (to)/from donor restricted operating funds</td>
<td>4 997 758</td>
<td>(516 872)</td>
</tr>
</tbody>
</table>

NET SURPLUS AFTER ALLOCATIONS

<table>
<thead>
<tr>
<th></th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

MMV CONSOLIDATED STATEMENT OF CASH FLOW FOR THE PERIOD ENDED

<table>
<thead>
<tr>
<th>(LOSS)/SURPLUS FOR THE YEAR</th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notes USD USD</td>
<td>2018</td>
<td>2017</td>
</tr>
<tr>
<td>CASH FLOW FROM OPERATING ACTIVITIES</td>
<td>12 169 127</td>
<td>3 728 802</td>
</tr>
<tr>
<td>Increase in Provisions</td>
<td>5 119 653</td>
<td>17 579</td>
</tr>
<tr>
<td>Depreciation</td>
<td>4 125 933</td>
<td>184 417</td>
</tr>
<tr>
<td>(Increase) / decrease in donations receivable</td>
<td>(6 256 419)</td>
<td>(405 620)</td>
</tr>
<tr>
<td>(Increase) / decrease in accounts receivable</td>
<td>(14 567 629)</td>
<td>3 067 558</td>
</tr>
<tr>
<td>(Increase) / decrease in accounts receivable due to reimbursement of prior years expenditures</td>
<td>-</td>
<td>925 567</td>
</tr>
<tr>
<td>(Increase) / decrease in tax receivable</td>
<td>(35 251)</td>
<td>4 217</td>
</tr>
<tr>
<td>(Increase) / decrease in project-related prepaid expenses</td>
<td>2 006 347</td>
<td>(1 240 854)</td>
</tr>
<tr>
<td>(Increase) / decrease in prepaid expenses</td>
<td>(197 570)</td>
<td>7 791</td>
</tr>
<tr>
<td>(Increase) / decrease in long term receivable</td>
<td>(14 213 484)</td>
<td>4 129 455</td>
</tr>
<tr>
<td>Increase / (decrease) in accrued R&amp;D commitments</td>
<td>5 296 902</td>
<td>171 834</td>
</tr>
<tr>
<td>Increase / (decrease) in accrued APM commitments</td>
<td>447 305</td>
<td>597 487</td>
</tr>
<tr>
<td>Increase / (decrease) in deferred revenue</td>
<td>8 19 470 549</td>
<td>-</td>
</tr>
<tr>
<td>Increase / (decrease) in other creditors</td>
<td>(227 431)</td>
<td>(413 910)</td>
</tr>
<tr>
<td>Increase / (decrease) in accrued expenses</td>
<td>156 747</td>
<td>206 272</td>
</tr>
<tr>
<td>Increase / (decrease) in donations reimbursement payables</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Unrealised foreign currency (gain) / loss</td>
<td>(79 841)</td>
<td>(489 007)</td>
</tr>
<tr>
<td>CASH FLOW RESULTING FROM OPERATING ACTIVITIES</td>
<td>4 216 938</td>
<td>10 491 588</td>
</tr>
</tbody>
</table>

CASH FLOW FROM INVESTMENT ACTIVITIES

| (Increase) / decrease in guarantees | 5 384      | (27 609)   |
| (Increase) / decrease in derivative financial instruments | 129 825    | (167 562)  |
| (Increase) / decrease in fixed assets | 4 (129 370) | (58 981)   |

CASH FLOW RESULTING FROM INVESTMENT ACTIVITIES

| 5 839                              | 254 152    |

NET INCREASE/(DECREASE) OF CASH AND CASH EQUIVALENTS

| 4 222 777                            | 10 237 436 |

Cash & cash equivalents at beginning of year

| 53 064 589                            | 42 328 666 |

Effect of exchange rate fluctuations on cash held

| 122 367                              | 496 487    |

Cash & cash equivalents at end of year

| 57 409 733                            | 53 064 589 |
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, MMV is monitored by the Swiss Federal Supervisory Board for Foundations.

The consolidated financial statements for the year ending December 31, 2018 were approved for issue by the MMV Board on 27 March, 2019.

b) Foundation capital

The foundation capital is fully subscribed at USD 4,000,000 as stipulated under the original legal statutes. Under normal circumstances, foundation capital may be used during the year to meet cash flow shortfalls, but should be replenished before closing at year end. Foundation capital, together with the residual operations reserve, 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 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 donor’s requirements.

2. ACCOUNTING PRINCIPLES APPLIED IN THE PREPARATION OF THE CONSOLIDATED 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 following exchange rates were used at year end:

2018
- CHF 1 = USD 1.016047
- EUR 1 = USD 1.144384
- GBP 1 = USD 1.273434
- AUD 1 = USD 0.705258

2017
- CHF 1 = USD 1.02423
- EUR 1 = USD 1.19786
- GBP 1 = USD 1.34912
- AUD 1 = USD 0.78049

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 at 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 2018:

<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. Delaware</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 the 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 the judgements made 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 at 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 one month after the closing date.

<table>
<thead>
<tr>
<th></th>
<th>2018 USD</th>
<th>2017 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash</td>
<td>6 685</td>
<td>5 836</td>
</tr>
<tr>
<td>Bank Balances</td>
<td>37 403 048</td>
<td>45 058 753</td>
</tr>
<tr>
<td>Money Market Deposits</td>
<td>20 000 000</td>
<td>8 000 000</td>
</tr>
<tr>
<td><strong>Total cash and cash equivalents</strong></td>
<td><strong>57 409 733</strong></td>
<td><strong>53 064 589</strong></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>2018 Fixtures &amp; Installations USD</th>
<th>2018 Office Furnitures USD</th>
<th>2018 Computers &amp; equipment USD</th>
<th>2018 Total USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs at 1 January 2018</td>
<td>798 948</td>
<td>403 255</td>
<td>393 522</td>
<td>1 595 725</td>
</tr>
<tr>
<td>Additions</td>
<td>107 048</td>
<td>-</td>
<td>22 322</td>
<td>1 297 370</td>
</tr>
<tr>
<td>Disposals</td>
<td>-</td>
<td>(6 045)</td>
<td>-</td>
<td>(6 045)</td>
</tr>
<tr>
<td><strong>At 31 December 2018</strong></td>
<td><strong>905 996</strong></td>
<td><strong>397 210</strong></td>
<td><strong>415 844</strong></td>
<td><strong>1 719 050</strong></td>
</tr>
<tr>
<td>Accumulated depreciation at 1 January 2018</td>
<td>737 127</td>
<td>388 049</td>
<td>298 432</td>
<td>1 423 608</td>
</tr>
<tr>
<td>Depreciation for the year</td>
<td>63 005</td>
<td>8 607</td>
<td>54 322</td>
<td>125 933</td>
</tr>
<tr>
<td>Disposals</td>
<td>-</td>
<td>(6 045)</td>
<td>-</td>
<td>(6 045)</td>
</tr>
<tr>
<td><strong>At 31 December 2018</strong></td>
<td><strong>800 132</strong></td>
<td><strong>390 611</strong></td>
<td><strong>352 754</strong></td>
<td><strong>1 543 496</strong></td>
</tr>
<tr>
<td>Net book value at 31 December 2018</td>
<td><strong>105 864</strong></td>
<td><strong>6 599</strong></td>
<td><strong>63 090</strong></td>
<td><strong>175 554</strong></td>
</tr>
</tbody>
</table>

### 5. 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>Balance at 1 January 2018</td>
<td>599 954</td>
<td>599 954</td>
</tr>
<tr>
<td>Use or 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><strong>703 624</strong></td>
<td><strong>703 624</strong></td>
</tr>
</tbody>
</table>
6. DONATIONS

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 13.

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 as 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 2018:

<table>
<thead>
<tr>
<th>Donor</th>
<th>Cash received 2018</th>
<th>Income recognised during previous year</th>
<th>Income to be received</th>
<th>Unrealized foreign exchange gain / (loss)</th>
<th>Total income as per statement of comprehensive income</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bill &amp; Melinda Gates Foundation</td>
<td>20 000 000</td>
<td>(810 000)</td>
<td>405 000</td>
<td>-</td>
<td>20 000 000</td>
</tr>
<tr>
<td>Bill &amp; Melinda Gates Foundation (Innovation Fund)</td>
<td>2 000 000</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 000 000</td>
</tr>
<tr>
<td>Global Health Innovative Technology (GHIT) Fund</td>
<td>1 768 996</td>
<td>(515 605)</td>
<td>81 200</td>
<td>-</td>
<td>1 334 591</td>
</tr>
<tr>
<td>Swiss Government (DEZA/SDC)</td>
<td>1 616 834</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 616 834</td>
</tr>
<tr>
<td>UK Government (DFID)</td>
<td>14 986 801</td>
<td>-</td>
<td>6 367 170</td>
<td>142 780</td>
<td>21 496 751</td>
</tr>
<tr>
<td>UK Government (Department of Health)</td>
<td>5 031 648</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5 031 648</td>
</tr>
<tr>
<td>US Government (USAID)</td>
<td>1 054 178</td>
<td>-</td>
<td>839 319</td>
<td>-</td>
<td>1 893 497</td>
</tr>
<tr>
<td>Irish Aid</td>
<td>1 164 839</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 164 839</td>
</tr>
<tr>
<td>Australian Government (DFAT)</td>
<td>2 822 678</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 822 678</td>
</tr>
<tr>
<td>German Government (BMBF)</td>
<td>467 101</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>467 101</td>
</tr>
<tr>
<td>Netherlands Government (OTA)</td>
<td>3 760 587</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 760 587</td>
</tr>
<tr>
<td>Monaco Government</td>
<td>118 399</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>118 399</td>
</tr>
<tr>
<td>National Institutes of Health (NIH)</td>
<td>30 900 (19 500)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11 400</td>
</tr>
<tr>
<td>Unilaid (Supply Grant)</td>
<td>1 279 691</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 279 691</td>
</tr>
<tr>
<td>Unilaid (RAS)</td>
<td>36 270 (36 270)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>World Health Organization (WHO)</td>
<td>169 500 (138 000)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>33 500</td>
</tr>
<tr>
<td>ExxonMobil Foundation</td>
<td>400 000</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>400 000</td>
</tr>
<tr>
<td>Newcrest</td>
<td>376 357</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>376 357</td>
</tr>
<tr>
<td>Johnson &amp; Johnson Corporate Citizenship Trust</td>
<td>666 500</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>666 500</td>
</tr>
<tr>
<td>Individual donors</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td><strong>TOTAL RECEIVED</strong></td>
<td><strong>58 561 283</strong></td>
<td><em>(1 517 375)</em></td>
<td><strong>7 692 689</strong></td>
<td><strong>142 780</strong></td>
<td><strong>64 879 378</strong></td>
</tr>
</tbody>
</table>

On the total donations recognised in the Consolidated Statement of Operations, USD 5 have been received through MMV, North America, Inc.
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 paediatric 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.

GSK and MMV have shared the cost of development of Krintafel over the period 2008-2018. Under the terms of the co-development agreement, as GSK has used the PRV, MMV is entitled to the refund of its share of the co-development costs from GSK. GSK has agreed to reimburse 50% of MMV cumulative costs from 2008 until 31 December 2018 in Q1 2019, 25% in July 2022 and the residual 25% in July 2023. The two latter payments might be subject to amendments to reflect any additional Krintafel development costs incurred by MMV after 1 January 2019.

The cumulative costs incurred by MMV on the development of Krintafel from 2008 to 31 December 2018, amount to USD 28,426,969. It has been agreed that MMV would receive from GSK in Q1 2019 50% of this amount, i.e. USD 14,213,484, which is booked as a "short-term receivable". As of 31 December 2018, MMV estimates that GSK’s two additional payments, due in July 2022 and July 2023 (booked as “long-term receivables”), would be for an amount of not less than USD 7,106,742 each.

In addition to the above-mentioned refund of Krintafel (tafenoquine) co-development costs from GSK, in 2018 MMV received the following revenue from partnerships: from Takeda in respect of the co-development of DSM265 for a total of USD 2,000,000 (2017: USD 2,000,000); from Sanofi in respect of the co-development of OZ439/ferroquine for a total of USD 779,818 (2017: USD 1,436,074); and from Janssen in respect of the co-development of P218 for a total of USD 531,989 (2017: USD 389,560); and from Shin Poong as refund of the Pyramax® FDA registration costs for a total of USD 445,697 (2017: 0). In 2017 MMV had received USD 727,976 from Merck KGaA related to the co-development of DDD1077498.

MMV plans to use the above-mentioned revenues from partnerships in support of its charitable mission.
Project-related variable expenditure includes all legal advice/services for contract negotiations (IPR), organization and travel for project meetings/reviews, MMV scientific personnel compensation and various scientific project consultancies. Expenditure for this MMV support totalled USD 17,793,774 and USD 15,633,829 in 2018 and 2017, respectively.

**Project reimbursements receivable**
These refer to unused funds remaining from 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.

### 10. PERSONNEL EXPENSES

There were 59.2 full-time permanent employees at 31 December 2018 (2017: 58.3), as well as 29.7 full-time temporary staff members (2017: 28.7).

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 jointly funded by contributions from MMV and its employees.

<table>
<thead>
<tr>
<th></th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capital ratio</td>
<td>103.0%</td>
<td>112.8%</td>
</tr>
<tr>
<td>Pension fund (asset) / liability</td>
<td>43</td>
<td>2,977</td>
</tr>
</tbody>
</table>

### 11. FOREIGN CURRENCY TRANSLATION DIFFERENCES FOR FOREIGN OPERATIONS

#### Financial Income

<table>
<thead>
<tr>
<th></th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derivatives fluctuation</td>
<td>30,670</td>
<td>403,988</td>
</tr>
<tr>
<td>Bank interests</td>
<td>151,722</td>
<td>90,652</td>
</tr>
<tr>
<td>Exchange gain from CHF</td>
<td>-</td>
<td>105,617</td>
</tr>
<tr>
<td>Exchange gain from EUR</td>
<td>88,390</td>
<td>342,315</td>
</tr>
<tr>
<td>Exchange gain from GBP</td>
<td>-</td>
<td>223,630</td>
</tr>
<tr>
<td>Exchange gain from AUD</td>
<td>-</td>
<td>148,545</td>
</tr>
<tr>
<td>Exchange gain from JPY</td>
<td>-</td>
<td>131,462</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>270,782</td>
<td>1,446,209</td>
</tr>
</tbody>
</table>

#### Financial Expenses

<table>
<thead>
<tr>
<th></th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derivatives fluctuation</td>
<td>164,163</td>
<td>236,426</td>
</tr>
<tr>
<td>Bank charges</td>
<td>40,303</td>
<td>40,748</td>
</tr>
<tr>
<td>Exchange loss from CHF</td>
<td>121,179</td>
<td>-</td>
</tr>
<tr>
<td>Exchange loss from GBP</td>
<td>292,523</td>
<td>-</td>
</tr>
<tr>
<td>Exchange loss from AUD</td>
<td>204,282</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>822,450</td>
<td>277,174</td>
</tr>
</tbody>
</table>

### 12. LEASES

Non-cancellable operating lease rentals are payable as follows:

<table>
<thead>
<tr>
<th></th>
<th>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 year</td>
<td>947,688</td>
<td>1,040,519</td>
</tr>
<tr>
<td>Between 1 and 5 years</td>
<td>4,381,325</td>
<td>5,042,431</td>
</tr>
<tr>
<td>More than 5 years</td>
<td>-</td>
<td>713,813</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5,329,013</td>
<td>6,796,764</td>
</tr>
</tbody>
</table>

### 13. 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>2018</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 year</td>
<td>68,630,204</td>
<td>70,280,712</td>
</tr>
<tr>
<td>Between 1 and 5 years</td>
<td>191,652,466</td>
<td>68,891,577</td>
</tr>
<tr>
<td>More than 5 years</td>
<td>18,400,000</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>278,682,670</td>
<td>139,172,289</td>
</tr>
</tbody>
</table>
14. DERIVATIVE FINANCIAL INSTRUMENTS
Derivative financial instruments used for hedging balance sheet items are recognized at fair value on the date a derivative contract is entered into and are recorded as other receivables or other current liabilities. Derivatives are subsequently remeasured to their current fair value on each balance sheet date, with unrealized gains and losses recognized in the income statement as disclosed in Note 9.

<table>
<thead>
<tr>
<th>Options currency transactions</th>
<th>Positive value</th>
<th>Negative value</th>
<th>Purpose</th>
<th>Positive value</th>
<th>Negative value</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Financial instruments</td>
<td>-</td>
<td>-</td>
<td>N/A</td>
<td>160 495</td>
<td>(30 670)</td>
<td>Hedging</td>
</tr>
</tbody>
</table>

MMV uses currency options to hedge its exposure to foreign currency risk.

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>2018 USD</th>
<th>2017 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Board members &amp; meetings</td>
<td>349 639</td>
<td>222 253</td>
</tr>
</tbody>
</table>

There were no loans to directors or executive officers for the years ended 31 December 2018 and 31 December 2017.

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 affairs. 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 bidding in 2017, KPMG have been reappointed as statutory auditors. The current lead auditor, Hélène BEGUIN, has acted in this capacity since 2017.

During the fiscal year 2018, MMV paid a total of USD 103,833 (2017 USD 70,160) to its auditors. This amount can be split as follows:

- Audit services (including special audit reports to donors): USD 91,444 (2017 USD 70,160)
- Other services: USD 12,389 (2017 nil)

20. SUBSEQUENT EVENTS
No events have occurred between the balance sheet date and the date of this report that require adjustment to, or disclosure in, these financial statements.
MMV Board 2018

Standing from left to right

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

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

Mr Dominique Limet, Former Chief Executive Officer, ViV Healthcare, London, UK

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

Mr Alan Court, Senior Adviser to the United Nations’ Secretary General’s Special Envoy for Health in Agenda 2030 and for Malaria, USA; Former Director of the UNICEF Programme Division in New York; Former Director of the UNICEF Supply Division in Copenhagen

Dr David Reddy, CEO, MMV, Switzerland

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

Dr Robert Newman, Director, Aspen Management Partnership for Health (AMP Health), The Aspen Institute; Former Director of Global Malaria Programme, World Health Organization

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

Ms Elizabeth Linder, Executive Director, Beautiful Destinations; Founder, The Conversational Century; Senior Consulting Fellow, Chatham House Director’s Office; former Politics & Government Specialist, Facebook (based in USA & 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; and Executive Secretary of The African Leaders Malaria Alliance, USA

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

Seated from left to right

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

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; and Executive Secretary of The African Leaders Malaria Alliance, USA

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; Board Member of Novo A/S and Exiqon A/S, Denmark

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 FDA; Former: Senior Director, Global Regulatory Affairs, GSK, USA

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 FDA; Former: Senior Director, Global Regulatory Affairs, GSK, USA

Ambassador Dr Konji Sebati, CEO, Innovative Pharmaceutical Association of South Africa

Defeating Malaria Together

Behind the scenes
**MMV North America Inc. Board**

- **Dr Dennis Schmatz**  
  President of the Board of North America Inc.; Former Vice President, Head of Tsukuba Research Institute, Merck-Banyu Research Laboratories, Japan

- **Dr David Bowen**  
  Independent Advisor, USA

- **Mr Alan Court**  
  Senior Adviser to the United Nations’ Secretary General’s Special Envoy for Health in Agenda 2030 and for Malaria, USA

- **Dr David Reddy**  
  CEO, MMV, Switzerland

- **Ms Wendy Taylor**  
  Former Director, Center for Accelerating Innovation and Impact at USAID, USA

**Expert Scientific Advisory Committee (ESAC)**

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

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

- **Dr Aileen Allsop**  
  Former Vice President for Science Policy, R&D, AstaZeneca, UK

- **Prof. Thomas Baille**  
  Dean Emeritus, School of Pharmacy, University of Washington, USA

- **Dr Tesfaye Biftu**  
  Distinguished professor, National institute of Pharmaceutical Sciences, Addiscombe Science and Technology University, Ethiopia

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

- **Robert Clay**  
  Consultant/Managing Director, Highbury, Regulatory Science Limited, UK

- **Dr Anne Cooper**  
  Programme Director, Heptares, UK

- **Prof. Brian Cox**  
  Professor of Pharmaceutical Chemistry, University of Sussex, School of Life Sciences, UK

- **Prof. Umberto D’Alessandro**  
  Director, MRC Unit, The Gambia; Prof. at LSHTM

- **Ms Delese Mimi Darko**  
  CEO, Safety Monitoring & Clinical Trials Division, Food and Drugs Authority, Ghana

- **Dr Michael Dunne**  
  Chief Medical Officer, Durata Therapeutics, USA

- **Prof. Katsumi Haldar**  
  Julius Newland Chair of Biological Sciences, Univ of Notre Dame, USA

- **Dr Monica Hemben Eimunjeze**  
  Director, Registration & Regulatory Affairs Directorate, National Agency for Food and Drug Administration and Control, Nigeria

- **Prof. Paul Fish**  
  Head of Chemistry, Alzheimer’s Research UK; UCL Drug Discovery Institute, UK

- **Prof. Daniel Goldberg**  
  Professor and Co-Chief, Division of Infectious Diseases, Department of Medicine, Washington University, USA

- **Dr Tim Hammond**  
  Independent Pharmaceutical Preclinical Safety Consultant at Preclinical Safety Consulting Ltd, UK

- **Dr Laurent Hennequin**  
  Research Director, Galderma R&D by Nestlé Skin Health/Galderma R&D France-Antipolis, France

- **Prof. Dennis Kyle**  
  Director, Center for Tropical and Emerging Global Diseases, University of Georgia, USA

- **Dr Marcus Lacerda**  
  Public Health Specialist, Flocrux, Brazil

- **Prof. John Lambert**  
  Chief Medical Officer, Global Head Medical Affairs and Consulting, PAREXEL International – Early Phase, UK

- **Dr Mary Mader**  
  Research Fellow, Discovery Chemistry Research and Technologies, Eli Lilly and Company, USA

- **Prof. Christine Manyando**  
  Tropical Diseases Research Centre, Zambia

- **Dr George Mooney**  
  KGM Pharma Consulting LLC, USA

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

- **Prof. Dennis Shanks**  
  Director, Australian Defence Force Malaria and Infectious Disease Institute, Australia

- **Dr Peter Siegl**  
  Siegl Pharma Consulting, USA

- **Prof. Dennis Smith**  
  Independent Consultant; Former VP, Pfizer Global R&D, UK

**Access & Product Management Advisory Committee (APMAC)**

- **Dr Richard Steketee**  
  MD, MPH, Chairman of MMV APMAC; Deputy Director, US President’s Malaria Initiative, USA

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

- **Dr Graciela Diap**  
  Associate Staff of DNDi and FACT Medical Coordinator, Spain

- **Dr Susanna Hausmann-Muela**  
  Chief Program Officer, Botnia Foundation, Switzerland

- **Prof. Corine Karema**  
  Swiss TPH, Switzerland; Malaria Expert on Global Fund Technical Review Panel; former Director NMCP, Rwanda

- **Ms Maeve Magner**  
  MBA, Supply Chain Expert, USA/Ireland

- **Dr Elizabeth Juma**  
  WHO Inter-country Support Team for Eastern and Southern Africa

- **Dr Corine Karema**  
  WHO Inter-country Support Team for Eastern and Southern Africa

- **Dr Wilfrid Mbacham**  
  Fellow CAS/AAS, Chair Dept of Physiology and Biochemistry, Univ of Yaoundé, Cameroon

- **Dr Kamini Mendis**  
  Independent Consultant in Malaria and Tropical Medicine, Sri Lanka

- **Prof. Dennis Smith**  
  Independent Consultant; Former VP, Pfizer Global R&D, UK

- **Dr Martin De Smet**  
  Coordinator of the Malaria Working Group of Médecins Sans Frontières

- **Dr Gagan Singh Sonal**  
  WHO, South-East Asia Regional Office

- **Prof. Andy Stergachis**  
  Director, Global Medicines Program, Univ of Washington, USA

**Global Safety Board**

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

- **Dr Stephan Duparc**  
  Co-Chairman of MMV Global Safety Board; Chief Medical Officer, MMV, Switzerland

- **Prof. Tim Hammond**  
  Pharmaceutical Preclinical Safety Consultant, UK

- **Prof. Pieter Joubert**  
  Clinical Pharmacology Consultant, UK

- **Dr John Pears**  
  Director, Woodhouse Green, UK

**Behind the scenes**
Franziska Karyabwite  
Executive Vice President,  
Head of Human Resources

Wiweka Kaszubska  
Vice President, Head of Product Development

Elizabeth Kernen  
Administrative Assistant

Benoit Laleu  
Associate Director, Drug Discovery

Melanie Larson  
Project Manager,  
Access & Product Management

Didier Leroy  
Senior Director, Drug Discovery

Peggy Letilly  
Travel Coordinator

Jorge Liz  
Senior Clinical Trial Manager

Andrea Lucard  
Executive Vice President, External Relations

Adrienne MacDonald  
Digital Communications Manager

Fiona Macintyre  
Senior Director, Clinical Sciences

Simona Mag Valigova  
Legal Counsel

Jean-Christophe Magnin  
Finance Officer

Maud Majeres Lugand  
Research & Projects Manager,  
Access & Product Management

Neil McCarthy  
Vice President, Head of External Relations

Jörg Möhrle  
Vice President, Head of Translational Medicine

Heidi Mostafa  
Legal Assistant

Allison Neapole  
Associate General Counsel

Alice Neequaye  
Quality Officer & Archivist

Thamayanthi Pasupathipilly  
Project Coordinator, Translational Medicine

Alcja Poczatenko  
Senior Legal Counsel

Abena Poku-Awuku  
Project Manager, External Relations

Elizabeth Poll  
Communications Manager

Hanu Ramachandruni  
Senior Director,  
Technical Product Development

Anya Ramalho  
Executive Vice President,  
Business Development

Valentina Rapillard  
External Relations Intern

David Reddy  
Chief Executive Officer

Wendy Redford  
HR Business Partner

Veronique Reusse  
HR Business Partner

Mélanie Rouillier  
Senior Project Coordinator, Discovery

Sahar Sabetnia  
Director, Business Development

Danielle Sessa  
Junior Communications Officer

Lindsay Seth  
Manager, Events and Travel

Ivana Sirovic Aplon  
Manager, Donor and Stakeholder Relations

Andrew Slade  
Director, Translational Medicine

Anouchka Smits Bayala  
Senior Product Development Coordinator

Tareq Sunderji  
Legal Administrative Officer

André-Marie Tchouatieu  
Associate Director,  
Access & Product Management

Anna Thomas  
Senior Director, Regulatory Lead

Belen Tornesi  
Senior Director,  
Non-Clinical Pharmacology & Toxicology

Florian Wartha  
Associate Director, Product Development

Helen Weir  
Personal Assistant to the CEO

Timothy Wells  
Chief Scientific Officer

Paul Willis  
Senior Director, Drug Discovery

Antonia Wolff  
Senior Project Coordinator,  
Translational Medicine
MMV is also grateful for the support received from private individuals.