Malaria
- takes a child’s life every minute of every day
- killed an estimated 627,000 people in 2020
- can kill within 24 hours of symptom onset
- is both a cause and a 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 underserved populations at risk of malaria, and help to ultimately eradicate this terrible disease.
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Malaria through an equity lens: meeting the goals for all

Message from the Chairman and CEO

In 2015, the United Nations adopted the 2030 Agenda for Sustainable Development and the Sustainable Development Goals (SDGs), calling for action by all countries to meet the comprehensive goals. Target 3.3 of the SDGs includes ending the epidemic of malaria.

MMV has been answering this call, working to ensure inclusivity and equity in its end-to-end mission to discover, develop and deliver critically needed new malaria medicines, in alignment with SDG 10 (to reduce inequalities). Despite the continued challenges brought on by the COVID-19 pandemic — which exposed the extent of inequity in public health — in 2021, MMV and partners remained committed to that mission and to placing the people most at risk, front and centre of its initiatives. At this, the halfway mark of the 2030 Agenda, it is a moment to reflect on the successes in the malaria fight and take stock of what remains to be done.

The case for malaria eradication has never been stronger

Over the last 20 years, the malaria community’s work saved an estimated 10.6 million lives and prevented ~1.7 billion cases. Yet, we were sobered by the data from the World Malaria Report (WMR) 2021¹ that the global burden of malaria is 12% more than in 2019 – an estimated 627,000 people lost their lives to the disease in 2020; of these, 96% were in Africa and 80% of those from Africa were young children. These statistics underscore the reality of the malaria burden and the need for the work of MMV and its partners to continue.

Seasonal malaria chemoprevention makes great strides

For 6 years, MMV has played a vital role in protecting children from malaria by implementing WHO-recommended seasonal malaria chemoprevention (SMC), sulfadoxine-pyrimethamine and amodiaquine (SPAQ). With partners, MMV helped over 33 million children in 13 Sahel countries receive SMC, ensured the scale-up of global and local manufacturers to provide over 100 million SPAQ courses and coordinated regional collaboration to routinely deploy the intervention.

SMC campaigns demonstrated the advantages of drug-mediated malaria prevention. Moreover, studies that combined SMC with the WHO-endorsed RTS,S vaccine² showed greater protection in children than either intervention alone, leading some countries to consider joint implementation.

Progress in the drive to push back resistance

Africa is facing the serious threat of resistance to artemisinin³. In 2021, MMV made progress in advancing next-generation antimalarial compounds to counter this threat. Notably, in September, MMV and Novartis reported positive Phase II results for ganaplacide-lumefantrine, a novel combination therapy for uncomplicated malaria in adults and children. Another Phase IIb study is ongoing.

Tackling inequity in public health

Inequity in public health is present at many levels. A recent FCDO strategy paper⁴, Ending preventable deaths of mothers, babies and children by 2030 reiterates

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¹ World Malaria Report 2021: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021
the enormous number of annual maternal, new-born and child deaths. Given that the population is at high risk of malaria, but has little in targeted treatment, MMV has prioritized meeting the needs of pregnant women and their babies.

Our Malaria in Mothers and Babies (MEMBAs) initiative aims to raise the standard of care for pregnant women and neonates affected by malaria. Activities include ensuring drug supplies, generating data on the impact of existing antimalarials, developing new medicines deemed low risk to the developing foetus and supporting the Speed Up Scale-Up Campaign⁵.

Furthermore, the MMV and Liverpool School of Tropical Medicine (LSTM) collaboration to establish pregnancy registries across sub-Saharan Africa is helping to fill the data gap on the use of antimalarials in pregnancy and will help us inform the development of appropriate options.

Initiatives to expand equitable access of P. vivax cures

In 2021, in collaboration with partners, MMV launched two new tafenoquine⁶-related programmes: the VivAction initiative to expand the suite of tools for P. vivax case management; and the implementation of the TRuST study – the first-ever evaluation of the use of tafenoquine in a real-world setting, to allow the Brazilian Ministry of Health (MoH) to decide whether to adopt the protocol nationwide.

Deepening our role in supply chain security

We are intensifying our focus on making antimalarial medicines more accessible, working with Kenya’s Universal Corporation Ltd., as well as Nigeria’s Emzor Ltd. and Swipha Ltd. to produce WHO-prequalified sulfadoxine-pyrimethamine to protect children and pregnant women.

A new resistance strategy

MMV’s new co-developed treatments are already saving lives while others are progressing through the pipeline. MMV continues to pioneer ground-breaking approaches to accelerate research into new compounds – for instance, a predictive assessment tool to gauge the risk of resistance of antimalarial compounds (p. 29).

Furthermore, in May 2021, *Trends in Parasitology* published MMV’s new strategy of resistance identification⁷ outlining early decision processes to stop/deprioritize a compound/series if a risk of drug resistance is identified. This tool will inform investment decisions and improve the quality of compounds over time from a resistance perspective.

Continuing support for the COVID-19 response

MMV continues to leverage its assets, partnerships and end-to-end capabilities in contribution to the ongoing COVID-19 response. This includes support for compound screening against SARS-CoV-2; support to modelling and simulation platforms to predict potential drug-drug interactions and drug concentrations in human lung epithelium for several antimalarials; as well as support for the progression into clinical development of two existing antimalarials.

A moment for reflection and gratitude

2021 saw the untimely loss of two much-respected MMV advisors; Ambassador Dr Konji Sebati, South African doctor, diplomat and MMV Board member; and MMV’s Access and Product Management Advisory Committee co-Chair Dr Martin de Smet, physician and malaria coordinator, Médecins Sans Frontières. These venerable members of MMV’s governing bodies dedicated their lives to improving the health of others and provided crucial leadership and guidance to MMV over many years. They will be sorely missed.

MMV extends its thanks to outgoing Chairman, Per Wold-Olsen for his superb leadership over the years and heart-felt appreciation goes out to Dennis Schmatz and Win Gutteridge who reached the end of their terms as Board members in 2021.

In conclusion, while we face great challenges, we have reasons to be optimistic. We grow stronger with our expanding network of partners. With continued collaboration, over the years we have saved almost 3 million young lives and brought forward 13 quality medicines.

This work could not have been done without the partnership of our funders. Funding remains a lifeline for all sections of the malaria community, including research and development, and we applaud the WMR’s call for donors to treble funding to meet the goals of the 2030 Agenda. The sustained commitment of MMV’s donors has enabled significant progress over the last 2 decades and is essential moving forward to keep the malaria portfolio populated, advance the development of new compounds through the pipeline and achieve a future where everyone has access to the malaria interventions they need.

Meanwhile, MMV continues to drive towards equity, building on successes and redoubling our focus on malaria eradication and the attainment of the SDGs. With our deep commitment to ending malaria, we are working with partners to keep the heartbeat of health strong among all those at risk of malaria, until that vision is eventually realised. •

Mr Alan Court
Chairman of the Board since September 2021

Dr David Reddy
CEO
Milestones 2021

The United Nations’ 2030 Agenda for Sustainable Development was adopted as a shared blueprint for peace and prosperity for people and planet. The goals call for urgent action to end economic and social challenges such as poverty, hunger, discrimination against women and girls, while improving health, education and tackling climate change. MMV and partners recognize that the 17 Sustainable Development Goals are integrated, that action in one area will affect outcomes in others, and that equitable development must balance social and economic sustainability. With a focus on our malaria work, in 2021, we also aimed to contribute to the achievement of several additional SDGs.

Access to affordable and effective antimalarials is key to eliminating malaria, a major cause of poverty. MMV has assembled the largest ever portfolio of antimalarials supporting target 3.3, which aims to end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases.

Availability of antimalarials for workers and their families in affected areas decreases absenteeism in the workplace. It also decreases absenteeism at school which fosters future work opportunities.

MMV prioritizes the needs of women and girls of reproductive age, a key population at risk of malaria. MMV invests in partnerships, including those which strengthen research and manufacturing capacity in Africa.

MMV’s vision is a world in which antimalarials cure and protect the most vulnerable and under-served populations. Partnership is at the core of the PDP model, bringing together academia, pharma, research institutes, philanthropic organizations and funders.

1 NO POVERTY
Access to affordable and effective antimalarials is key to eliminating malaria, a major cause of poverty.

3 GOOD HEALTH AND WELL-BEING
MMV prioritizes the needs of women and girls of reproductive age, a key population at risk of malaria.

5 GENDER EQUALITY
Availability of antimalarials for workers and their families in affected areas decreases absenteeism in the workplace. It also decreases absenteeism at school which fosters future work opportunities.

8 DECENT WORK AND ECONOMIC GROWTH
MMV invests in partnerships, including those which strengthen research and manufacturing capacity in Africa.

9 INDUSTRY, INNOVATION AND INFRASTRUCTURE
MMV’s vision is a world in which antimalarials cure and protect the most vulnerable and under-served populations.

10 REDUCED INEQUALITIES
Partnership is at the core of the PDP model, bringing together academia, pharma, research institutes, philanthropic organizations and funders.

17 PARTNERSHIPS FOR THE GOALS

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450 million Coartem® Dispersible (artemether-lumefantrine) paediatric treatments distributed in over 50 countries since 2009, saving more than 960,000 children’s lives

255 million vials of injectable artesunate delivered since 2010, saving an estimated 1.66 million additional lives compared to treatment with injectable quinine¹

8.6 million Eurartesim® (dihydroartemisinin-piperaquine) treatments distributed between 2011 and 2021

7.6 million artesunate rectal capsules distributed since 2018, saving more than 780,000 lives

2.8 million Pyramax® (pyronaridine-artesunate) treatments delivered to date, with registration in 29 countries – of which about half were the paediatric granules formulation

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¹ Assuming that patients would have received injectable quinine in the absence of injectable artesunate.

² Knowledge sharing for severe: https://www.severemalaria.org/
540 million ASAQ Winthrop® treatments delivered to date, with registration in 33 countries

728 million courses of sulphadoxine-pyrimethamine and amodiaquine (SPAQ) have been delivered since the launch of seasonal malaria chemoprevention (SMC) in 2014. In 2021 alone, over 44 million children in 13 countries were protected

Kozenis/Krintafel (tafenoquine) received regulatory approval in Peru for prevention of P. vivax relapse

The Partnership for Vivax Elimination (PAVE) was launched in 2021 with PATH, Menzies School of Health Research and the Burnet Institute to accelerate elimination of relapsing of P. vivax malaria

B&O Pharma selected as a manufacturing partner for low-dose primaquine for the prevention of relapse P. vivax malaria

Ganaplacide-lumefantrine yielded positive results in a Phase IIb trial, supporting the continued development of the combination for uncomplicated malaria

ZY19489 + ferroquine yielded positive results in Phase I studies, demonstrating potent antimalarial activity

TRuST feasibility study, representing first real-world application of tafenoquine, began in September 2021 with interim results received in December

One pregnancy registry established in Kenya, with permission granted for expansion to Burkina Faso

M5717 + pyronaridine selected as a new combination for development

GSK484 selected as MMV’s Project of the Year 2021

IWY357 selected as a new candidate for development

Studies have shown the zebrafish assay to be a reliable tool for the prediction of embryotoxicity in mammals, which could help pave the way for earlier inclusion of pregnant women in clinical trials

MMV has built an extensive network of over 400 partners in 50 countries since its inception in 1999

Technology transfer resulted in the opening of a testing centre for resistance profiling in Burkina Faso
ALMA is a coalition of 49 African heads of state and government established in 2009 and working across country and regional borders to eliminate malaria by 2030. It was inspired by the African Union vision of an Africa free of malaria and guided by the World Health Organization’s Global Technical Strategy for Malaria 2016–2030.

Agenda 2063: The Africa We Want: https://au.int/en/agenda2063/

Message from Ms Joy Phumaphi, Executive Secretary of the African Leaders Malaria Alliance and MMV Board Member

The latest World Malaria Report was a wake-up call – we have underestimated the global burden of malaria for over two decades. Although the decline in malaria cases and deaths was real, the actual baseline numbers were 28.7% higher than we had previously calculated. In 2020, the year that the COVID-19 pandemic threw its deadly pall over the world, an estimated 627,000 people lost their lives to malaria, 93% of whom lived in Africa, and the vast majority were children under 5 years of age.

Lessons from COVID-19 – a blueprint for Africa’s malaria programme

The global response to COVID-19 has shown that in the face of a global crisis, governments can launch unprecedented collaborations at breathtaking speed. It has also shown us that a massive influx of global resources by motivated governments, fast-tracked regulatory approval, as well as research and development of new treatments and vaccines were not only possible but critical to getting the pandemic under control.

Unfortunately, COVID-19 has also reminded us that the uneven distribution of wealth and access to treatment has left many poorer countries struggling to secure needed vaccines and medicines, including essential malaria commodities. Renewed calls for a more balanced distribution of research and manufacturing investments to address global health threats apply equally to COVID-19 and malaria.

Undeterred in the face of new challenges

Over the last 20 years, global efforts saved an estimated 10.6 million lives and prevented ~1.7 billion cases of malaria. As of 2015, the gains began to plateau and from 2020 onwards efforts were further challenged by COVID-19. Yet, in the words of His Excellency President Uhuru Kenyatta, Chair of the African Leaders Malaria Alliance (ALMA),1 we kept “the fire burning in the fight against malaria”.

Undaunted, we ensured that critical malaria programmes, such as mosquito-net distribution and indoor residual spraying were implemented, despite strict COVID-19 restrictions and supply chain disruptions across the globe. Similarly, seasonal malaria chemoprevention campaigns, in which MMV played a key role, also went ahead, protecting 33 million young lives, more than ever before. We cannot afford to slow this momentum if we intend to achieve the African Union Catalytic Framework to End AIDS, TB and Eliminate Malaria in Africa by 2030, Agenda 2063,2 and the United Nations Sustainable Development Goal to end malaria by 2030.

1 ALMA is a coalition of 49 African heads of state and government established in 2009 and working across country and regional borders to eliminate malaria by 2030. It was inspired by the African Union vision of an Africa free of malaria and guided by the World Health Organization’s Global Technical Strategy for Malaria 2016–2030.
2 Agenda 2063: The Africa We Want: https://au.int/en/agenda2063/ overview
Averting further setbacks in the fight against malaria

The urgency that drove the global COVID-19 response underscored four major requirements to achieve these goals: a stronger supply chain from end to end; equitable access to medical commodities; open multisectoral collaboration to enable technology and knowledge transfer; and extensive and sustained funding. The first two of these can be attained by locally manufacturing quality-assured health commodities in Africa. The continent is moving towards producing its own quality medicines, accelerating the implementation of the Pharmaceutical Manufacturing Plan for Africa business plan, and has established the African Medicines Agency. This will help address the supply chain and improve regulatory harmonization across the continent. These ongoing efforts will grow Africa’s ability to manufacture the antimalarial medicines to meet its massive need.

Africa is boosting initiatives against malaria

As the COVID-19 pandemic and its repercussions continue to upend lives and economies across the world, Africa has not lost its focus on defeating malaria and is taking action on several fronts. Regional economic communities are working to ensure the harmonious implementation of continental policies and regional programmes. Newly energized plans are building the scientific capacities of African research and public health institutions with stronger research training programmes. Evidence collected on the specific needs of the population and gaps in commodities and key materials will be shared with the pharmaceutical industry. Stronger regulatory and policy frameworks will enable harmonized quality-assured drug development, and technical support will help local manufacturers upgrade to international quality standards.

Need for a strong and secure African pharmaceutical supply chain

Meeting the health needs of Africa’s growing population will require a strong and secure supply chain for health commodities. To ensure easy access to treatment, drugs, vaccines and vector control commodities must be produced closer to patients and communities in need. Growing the numbers of well-regulated African pharmaceutical companies to manufacture quality-assured medicines will help address this concern and make low-cost, generic, quality antimalarial medicines affordable and accessible to all.

This is especially true on the continent which currently imports between 70% and 90% of its total medicines, compared to 5% in China and 20% in India. African governments are calling for domestic and international investment to strengthen local manufacturing, given that only five of the 375 drug manufacturers on the continent meet global quality standards, such as World Health Organization (WHO) prequalification.

Recognizing the urgent need to stabilize the antimalarial supply chain and diversify supply, in addition to continuing its work to discover and develop new antimalarials, MMV has been supporting manufacturers in Kenya and Nigeria to secure WHO prequalification for medicines that help prevent malaria in pregnant women and children; MMV is also assisting two South African organizations to strengthen their manufacturing capacity.

Funding and collaboration are the cornerstones of change

Having witnessed the incredible return on investment for COVID-19 diagnostics, vaccines and treatments, we hope that research funders will expand their investments in vaccine and drug development for infectious diseases, like malaria. Over the years, the malaria community has been functioning on half the resources required annually to help eliminate malaria by 2030. An increase in funding will drive us closer to that goal.

As executive secretary of ALMA, I would like to emphasize that in seeking greater autonomy, the programme to expand African manufacturing must be led by African leaders as it concerns the development of our continent and the well-being of our people. To this end, ALMA is calling for accelerated support and domestic funding to add more power to the engine.

Exemplifying the need for Africans to take responsibility in accelerating the drive to end malaria, 23 African countries are engaging communities and leaders to support the Zero Malaria Starts with Me campaign. To end malaria, we must collaborate not just with our partners, the African Union Development Agency, all African regional bodies, the Africa Centres for Disease Control and Prevention, but also with committed product development partnerships like MMV. Zero Malaria Starts with me!

“MMV has been supporting manufacturers in Kenya and Nigeria to secure WHO prequalification for medicines that help prevent malaria in pregnant women and children”
Tackling inequity in health

Shining a light on the most at risk

Malaria is still a leading cause of death in many least-developed countries. Even though anyone may be infected by malaria, there are some groups that are at greater risk than others. In 2020, a staggering estimated 11.6 million pregnant women were infected with malaria in sub-Saharan Africa, with devastating consequences for both mothers and babies. Pregnancy reduces a woman’s immunity to the parasite, making her more at risk of developing infection and exposing her unborn baby to the adverse effects of an infection during pregnancy, effects that can include premature delivery or stillbirth, and low birth weight.

Children under 5 years of age are another segment of the population at high risk of being infected by malaria and developing complications, accounting for about 80% of all malaria deaths in sub-Saharan Africa. Besides these groups, malaria is among the top killers of adolescent girls, and contributed to 7.4% of deaths among this population, with younger pregnant adolescents being at a higher risk of malaria and anaemia. Programmes that take these populations into consideration and invest in research and development of therapies that are well tolerated by pregnant women are necessary to better serve these populations.

MMV’s MiMBa strategy: meeting the needs of pregnant and lactating women

The Malaria in Mothers and Babies (MiMBa) initiative aims to improve care for pregnant and lactating women and their newborns. First, by ensuring that the right quality-assured medicines are available and accessible to them. Then, by prioritizing and accelerating the development of new antimalarial medicines that are appropriate for use in all stages of pregnancy and promoting an earlier inclusion of pregnant women in drug development. This ensures that innovative and appropriate medicines for pregnant and lactating women are developed to adequately serve them.

Closing the data gap: a step towards better antimalarials for pregnant women

Little information is currently available on malaria drug safety in the first trimester of pregnancy. As part of the MiMBa strategy, MMV and the Liverpool School of Tropical Medicine (LSTM) are collaborating to establish a pregnancy registry in malaria-endemic countries. Using the registry, the team is collecting information on the use of over-the-counter drugs and prescription medicines (including artemisinin-based combination therapies: ACTs) by pregnant women to treat uncomplicated and severe malaria. This information is added to the registry and linked to any outcome observed in the mother and newborn babies. One of the main goals of this project is to produce evidence-based information on the safety of first and second-line ACTs to treat uncomplicated malaria in pregnant women, particularly in the first trimester. The project is about to complete its first full year and the women who provided the initial data have already delivered their babies. The health profile of these babies is being closely monitored and documented. Only by knowing what pregnant women experience when taking antimalarial drugs, especially new drugs such as the most recently approved ACT, Pyramax® (pyronaridine-artesunate), and how their babies then develop, will it be possible for agencies such as the World Health Organization (WHO) to update their guidelines on well-tolerated drugs that can be used to treat and prevent malaria in this population.
Dr Hellen Barsosio, Senior Clinical Research Scientist, KEMRI/CDC/LSTM Collaboration (KCL), discusses her work on the MiMBa pregnancy registry.

**Why are pregnancy registries so important?**

Pregnancy registries are vital in providing safety information on drugs and vaccines used during pregnancy, particularly within the first trimester, a critical period for the growing baby. There is usually limited data on the safety of drugs by the time they come to the market, and little if any data at all about the safety in pregnancy; therefore, pregnancy registries are crucial to monitor safety in the early post-marketing phase. This information also helps to update drug labelling.

**How is the data from the registries collected?**

We collect information on exposure to prescription and over-the-counter drugs used to treat malaria and other illnesses from women of reproductive age, and link this to information we collect about pregnancies and pregnancy outcomes of interest, such as miscarriage and stillbirths, and from newborn babies at the end of pregnancy including any congenital malformations. We use multiple data sources to ascertain drug exposure, such as data from health facility registers, and interview women attending antenatal clinics at each visit, and at delivery, to inquire about recent drug exposure. We screen newborn babies at delivery and at 6 weeks of age for congenital anomalies. In addition, we will follow a sub-cohort of infants who were exposed to antimalarials in utero\(^6\) at 6 months and 1 year of age to screen for congenital anomalies not detected at birth, including congenital heart defects, and assess their neurodevelopment.

**What challenges did COVID-19 pose?**

The COVID-19 pandemic posed multiple challenges. First, we noted reduced antenatal clinic attendance among pregnant women, especially during the 3\(^{rd}\) and 4\(^{th}\) waves of the pandemic in Kenya. During these periods, we had to adapt the implementation of the study to ensure that staff, participants, and community health workers (CHWs) remained safe, breaking up the field teams to work in cohorts, restricting meetings, and providing masks and hand sanitizer to all staff, including all of the 400 CHWs working closely with the study. Second, we had multiple industrial strikes that interrupted the registry’s data collection activities in government hospitals, but we ensured our presence in private health facilities to which patients were diverted, to minimize gaps in the data. Third, some of our staff, research participants, CHWs and community health volunteers also fell ill. Thankfully, we now have free COVID-19 vaccines available to CHWs and the general population including pregnant women, in local health facilities. The cost of personal protective equipment has also substantially fallen and is now more readily available at hospitals and to the public, which has improved working conditions in medical facilities.

**What are the next steps?**

As of February 2022, we are entering the 11\(^{th}\) month of data collection, with one big push for recruitment and pregnancy detection for the last few months of another multiple first-line ACT study – conducted in parallel in the same region as the pregnancy registry – and ending in June 2022. We have also started active data cleaning and merging multiple data sources, including exploring integration with newly introduced electronic medical record systems’ in the study area. Some of our research participants have delivered their children, so we have started to document the babies’ health, including screening for congenital anomalies such as heart defects, and will shortly begin assessing neurocognitive development in a sub-cohort. By October 2023, we should have completed data collection and soon after we will analyse the data and share our findings.

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

I have to say that this has been one of my favourite collaborations of my career so far. MMV has been a true partner, and it has been an equitable and supportive collaboration. MMV has been hands on and supportive with the field teams led by the Kenya Medical Research Institute and LSTM, sharing their ideas, expertise, and checking in on our progress through joint project meetings. Dr Stephan Duparc from MMV recently visited our project sites in rural Homa Bay and on the islands in Lake Victoria involved in the study, meeting our staff, CHWs and field workers, experiencing the fieldwork that goes into the MiMBa Pregnancy Registry. This was special for us as we rarely experience this level of hands-on collaboration from Global North collaborators and funding partners.
Strategies to improve access of preventive options for pregnant women

MMV has prioritized the unmet needs of pregnant women and their babies. The WHO recommends the use of intermittent preventive treatment in pregnancy (IPTp) with three or more doses of sulfadoxine-pyrimethamine (SP) given to all pregnant women living in areas of moderate-to-high malaria transmission in Africa. The preventive treatment should start as early as possible in the 2nd trimester and can be administered at monthly intervals up to the time of delivery, to prevent the complications caused by malaria during pregnancy.\(^8\) There is a great lack of quality-assured SP for IPTp that is produced anywhere on the continent of Africa. To ensure that all pregnant women have access to quality-assured SP, MMV is engaged with three African manufacturers, Emzor Ltd. and Swipha Ltd. in Nigeria and Universal Corporation Ltd. in Kenya (p.24), to support their efforts to achieve WHO prequalification of their SP product for IPTp.

Studies have shown that despite an increase in coverage of WHO-recommended IPTp over the last decade, only a third of pregnant women in Africa have access to full (repeated) chemoprevention treatment over the course of their pregnancies.\(^9\) This lifesaving antimalarial treatment is given during antenatal care (ANC) visits to the ANC clinics. A promising approach to increase adherence to IPTp has been the delivery of preventive treatment by trained CHWs (C-IPTp).\(^10\) Transforming Intermittent Preventive Treatment for Optimal Pregnancy (TIPTOP)\(^11\) is a pilot project – in Democratic Republic of Congo, Madagascar, Mozambique and Nigeria – that aims to dramatically increase the number of pregnant women in malaria-affected countries in sub-Saharan Africa receiving antimalarial preventive therapy, thus saving the lives of thousands of mothers and newborns.\(^12\) With TIPTOP, MMV and project lead partners have set the stage for the scale-up of community distribution of IPTp with quality-assured SP to make sure the high demand is matched by a continuous and high-quality supply of the medicine. The TIPTOP project also involves carrying out research and household surveys to produce data on drug resistance and the cost-effectiveness of the initiative. It is hoped that data obtained with these studies will provide evidence to inform WHO’s implementation guide.

To ensure that all pregnant women have access to quality-assured SP, MMV is engaged with three African manufacturers... to support their efforts to achieve WHO prequalification of their SP product for IPTp.”
What is the goal of the TIPTOP pilot project?

We aim to build evidence for C-IPTp so that WHO and countries can review and potentially adopt C-IPTp as a delivery mechanism as part of malaria in pregnancy programming, helping achieve higher coverage of interventions globally. We also aim to set the stage for scale-up across the countries we target and with influence across sub-Saharan Africa.

How does the project break down barriers between pregnant women and the malaria medicines they need?

TIPTOP was designed as a ‘no missed opportunities approach’ so that eligible pregnant women have access to IPTp with quality-assured SP in the communities in which they live as well as at antenatal care clinics. To gain the trust of pregnant women, their families and the broader community, we worked with health workers who were selected by the community, along with local organizations. Pregnant women were counselled through CHWs and messaging about ANC, whilst malaria prevention, including IPTp, was reinforced through civil society organization platforms and other communication channels.

How will the evidence generated through this project be used?

The WHO will assess the data to determine whether it can be used to update its implementation recommendations (the ‘how to’). Countries will apply the learning to expand and scale up C-IPTp as well as introduce C-IPTp in countries where it has not yet been started.

What key challenges do you face?

The first challenge we face is keeping our CHWs and volunteers motivated. We also have the task of maintaining strong data systems that link community- and facility-level monitoring. Outside of TIPTOP (since we supplied the drug), but across sub-Saharan Africa, we face the challenge of availability of quality-assured SP at antenatal care clinics. With continued country and partner commitment, I believe these barriers can be overcome.

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

While MMV’s scope in the TIPTOP project was specific to the drug, we have (from the conceptualization phase) worked hand in hand to design, problem solve and meet the needs of the countries we support. It has been a true privilege to work with MMV.
Sustainable severe malaria case management

If not treated within 24 hours, malaria can progress to severe illness, sometimes with fatal consequences. It continues to take the life of a young child every minute of every day.13

In 2011, the World Health Organization recommended injectable artesunate as the preferred treatment for severe malaria in adults and children. With support from MMV, Fosun Pharma (China) became the first manufacturer to achieve WHO prequalification for this formulation in 2010. However, even with this breakthrough, patients continued to die because they lived too far from health facilities where healthcare professionals could administer injectable artesunate. With funding from Unitaid, MMV has worked in partnership with two Indian manufacturers – Cipla and Strides – to develop artesunate rectal capsules (also known as rectal artesunate – RAS),14 an easy-to-administer pre-referral intervention that can be administered by community health workers, buying enough time to transfer patients to a health facility to receive injectable treatment.

In parallel to developing RAS, in 2017 MMV joined forces with partners13 on a pilot project – MAM Against Malaria (MAM) – in the Serene District, Zambia,16 to improve severe malaria case management in children less than 6 years old. The project initially introduced RAS 100 mg, covering Serene’s population of 54,000 people. By 2018, this project had successfully reduced severe malaria case fatality by 96% (from 96 anticipated deaths to three).17,18 This was achieved not only through increased access to key medicines for severe malaria but also through effective community engagement, a functioning drug supply chain and an innovative emergency transport system for patients using bicycle ambulances.

The dramatic reduction in case fatality demonstrated the undeniable benefit of using RAS in tandem with emergency transport, creating a bridge to follow-up care with injectable artesunate followed by a full course of an ACT.

In 2019, the Zambian National Malaria Elimination Centre (NMEC) designed a new strategic malaria elimination plan that aligned the case management of severe malaria with WHO recommendations.19 Following the success of the 1-year MAM project funded by MMV and Transaid, the NMEC, together with MMV and partners Development Data, DAI Global Health, and Disacare, began working on scale up with additional funding from the FIA Foundation, Grand Challenges Canada and the government of Canada.20

By mid-2021, the NMEC began to scale up RAS to a further 26 districts,21 putting the government on course to reach approximately 22% of the country’s population. Training continues to be a key part of this expansion. For maximum coverage, the NMEC hopes that one day, initiatives similar to MAM will be present in all 114 districts of Zambia.24

MAM and MAM@Scale have shown the value of investing in communities and have empowered rural Zambian families to reduce the mortality risk to their children from severe malaria.25 Interventions implemented to generate community ownership and ensure the health system is responsive to community needs, have far-reaching and sustainable benefits. This approach changes the way a health system operates – it becomes truly people-centred, as envisioned in the Sustainable Development Goals.

In addition to the scale-up of RAS to treat severe malaria, MMV’s work in field stability testing of the drug has also borne fruit: the evidence led WHO to change their guidelines (2021)20 and recommend that CHWs can use the product for up to 6 months even if the ambient temperatures exceed 30°C. This is excellent news for the case management of severe malaria patients.

In 2021, observational research funded by Unitaid (The CARMAL Project27) raised concerns about the effectiveness of RAS in real-life settings, particularly when referral processes and quality of care could not be assured. Subsequently, WHO issued an information note28 in 2022 that advised countries employing RAS to ensure that its minimal use conditions were met, including: (i) correct diagnosis and administration of RAS; (ii) immediate referral; and (iii) treatment with injectable artesunate followed by a three-day ACT. For countries not yet using RAS, WHO advised waiting for further guidance from themselves. WHO will conduct a formal evidence review and develop detailed guidance on the conditions under which the use of this tool can be implemented safely and effectively. These recommendations point to the need to strengthen referral systems, inpatient care, and post-discharge planning. These critical elements of the “severe malaria patient journey” highlight the essential need for integrated health system planning and coordination to assure minimum standards of quality care under demanding real-life conditions.
Justina and her husband, Kelvin, are farmers who grow maize and soya beans in the Serenje District in Zambia’s Central Province. The malaria burden here is high which is why it was selected as the location for the MAMaZ Against Malaria project.

One day while Kelvin was out, Annette, one of the couple’s five children, developed a high fever. Later that day, her symptoms worsened: she began vomiting and having diarrhoea. “I was very scared because that day I was alone. My husband had gone to a funeral, so I was the only one that remained with the kids,” Justina says.

The next morning, Justina took Annette to visit the local community health volunteer (CHV), Charity. Justina says that by the time she reached Charity’s house, “my child was unconscious. She had no energy... I did not know [if] she would survive.”

Charity examined Annette and discovered that she was suffering from severe malaria. She gave Annette RAS and an oral rehydration solution, and to her mother, a referral slip to a health facility. Justina rushed Annette to the health facility by bicycle ambulance. When they arrived, Annette was taken straight to the clinical officer who admitted her immediately. She was given injectable artesunate and other therapies at the clinic, where Annette and Justina remained for 4 days. The treatment was concluded with a 3-day course of ACT.

This was the first time that any of Justina and Kelvin’s children had suffered from malaria, and they are grateful for lifesaving interventions, especially RAS and the bicycle transport, that are provided to the community by CHVs.

“This was the first time that any of Justina and Kelvin’s children had suffered from malaria, and they are grateful for lifesaving interventions, especially RAS and the bicycle transport, that are provided to the community by CHVs.

“Without the CHV,” Justina says, “my child would have died. The challenge is how do you move a sick child from here in the community to the facility? With the help of RAS and the CHVs, it is easier now. We feel confident as parents that our children will survive episodes of malaria.”
Seasonal malaria chemoprevention: protecting more children from malaria

Children under 5 are among the most vulnerable to malaria infection and its associated complications. To protect this population, WHO recommends seasonal malaria chemoprevention (SMC) – the administration of a combination therapy of sulfadoxine-pyrimethamine plus amodiaquine (SPAQ) to children aged 3–59 months in a 3-day regimen; it is typically administered at monthly intervals for up to 4 months during the rainy season when malaria transmission spikes.

When tested in clinical trials, SMC proved highly effective, providing up to 88% protection against malaria infection within the first 28 days after its administration, as shown in a recent case-control study with 2,126 malaria cases.

**SMC-Impact**, a project implemented by MMV and partners, seeks to assess the efficacy and cost-effectiveness of increasing the reach of SMC from children aged 3–59 months to children aged between 5 and 10 years in the Sahel region. Data from Senegal suggest that SMC in children up to 10 years of age is as effective, and as cost effective, as for children under 5 years of age.

As a result, at least three countries are now considering increasing the age limit: Mali, Burkina Faso and The Gambia. Among other objectives, the project also aims to evaluate the impact of adding an extra month of SMC coverage (from the typical 3–4 months) during the transmission season. This proposal is partly attributed to climate change, which is causing a shift in rainfall patterns and thus extending the malaria transmission season or causing a shift in malaria geographies. Beyond the SMC-Impact project, investments in research and modelling tools to determine shifts in rainfall patterns and their impact on malaria epidemiology are needed.

**OPT-SMC**: to ensure optimal delivery and effectiveness of SMC, MMV teamed up with key partners on the “Optimizing Impact of SMC” project. The project, led by the University of Thies in Senegal, aims to strengthen the capacity of National Malaria Control Programmes to conduct implementation research, to adapt SMC to the local context, and to improve its delivery and impact.

By 2020, MMV and its partners had established an SMC data capture tool to help countries plan and coordinate their campaigns and reach as many eligible children as possible. The data from this tool have since been used to compile the annual WHO World Malaria Report. In 2021, thanks to the remarkable efforts of the SMC Alliance partners, the SMC programme reached over 44 million children.

In addition, in October 2021, WHO recommended the world’s first malaria vaccine, RTS,S, developed by GSK, for use in children at risk in sub-Saharan Africa and other malariaous regions. A recent study showed that combining RTS,S with SMC in high transmission areas was markedly superior to either intervention alone at preventing severe malaria, and could further reduce malaria deaths by 70%. This integrated approach could be key to saving many more young lives.
How effective has SMC been in reducing child morbidity and mortality from malaria in Nigeria?

No formal impact assessment has been done in the country. However, a case-control study in five countries, including Nigeria, looked at the reduction in clinical malaria during the 4 weeks after receiving SMC with SPAQ. The protective effect reported from the Nigerian study arm was 83.1%. However, a landmark publication in *The Lancet* puts the reduction in confirmed malaria cases at outpatient clinics during the high transmission period at 55.2% in Nigeria.

Can you talk us through Nigeria’s expansion of the SMC programme?

In 2020, the nationally-led ‘high burden to high impact’ approach recommended by WHO to jump-start progress against malaria led to an expansion of SMC-eligible states; from nine states within the Sahelian region to 20, plus the Abuja Federal Capital Territory. In addition, in some of the new states, the cycles were increased from four to five due to extended annual rains.

What key challenges did you face in 2021 with regard to SMC implementation?

The COVID-19 pandemic posed new challenges affecting how we implemented SMC; personal protective equipment was required as well as specific training, which increased the unit cost of implementation.

How did you overcome these challenges?

We have mainstreamed COVID-19 preventive measures into the SMC training modules. Caregivers were asked to administer SPAQ with community distributors observing the process; supervisors also ensured physical distancing was respected, as well as adherence to precautionary actions by people and communities to help slow down the spread of COVID-19.

What has it been like to work with MMV on SMC?

The cooperation with MMV has been rewarding. Regular calls provide the opportunity for cross learning amongst SMC countries and this has provided information about new developments within the malaria sector.
Advancing malaria interventions while supporting the COVID-19 response

Solutions to address the emergence of artemisinin partial resistance in Africa

Artemisinin-based drug combinations were a significant addition to the antimalarial toolbox when introduced in 1971 as a first-line treatment for malaria. Alongside other malaria control tools they have contributed to driving down the disease burden, by 27% between 2000 and 2020. Despite the recent emergence of the parasite’s partial resistance to artemisinin, there is no call for panic. Instead, we need to implement three strategies. First, ensure only quality assured, recommended treatments are used. Second, implement strategies such as the use of multiple first-line therapies and low-dose primaquine to help mitigate the threat of resistance. Third, monitor for resistance and change treatments when resistance arises. Finally, ensure that there is a robust pipeline of next-generation drugs to replace today’s medicines when they eventually succumb to resistance.

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

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

Positive clinical results from a novel combination therapy

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

Unlike most drugs currently in use against malaria, ganaplacide is not an artemisinin derivative but rather an imidazolopiperazine that acts on an alternative molecular target yet to be identified, though with a novel Plasmodium falciparum cyclic amine resistance locus marker, and it is fully active on strains of malaria in drug-resistant patients. Indeed, ganaplacide is effective even against parasite strains carrying the Kelch 13 mutation that is strongly associated with artemisinin partial resistance.

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

2 World malaria report 2021: Global messaging: https://www.who.int/publications/m/item/WHO-UCN-GMP-2021.08
3 Refers to the situation where treating a patient with a first drug confers changes in the physiology of the tumor that reduce the efficacy of a second, unrelated drug that may be administered at a later time (100)
4 Pan-active imidazolopiperazine antimalarials target the Plasmodium falciparum intracellular secretory pathway: https://www.nature.com/articles/s41467-020-15440-4
5 Mutations in the Plasmodium falciparum cyclic amine resistance locus (PfCARL) are associated with parasite resistance to the imidazolopiperazines, a potent class of novel antimalarial compounds that display both prophylactic and transmission-blocking activity, in addition to activity against blood-stage parasites
6 The Kelch 13 gene is strongly associated with artemisinin partial resistance as defined by a ring-stage assay in vitro and delayed clearance in patients from Southeast Asia.
What did the results reveal from the Phase IIb study of the novel ganaplacide-lumefantrine combination in young children with malaria?

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

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

What is exciting about this combination?

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

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

What additional challenges were posed by COVID-19?

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

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

What are the next steps?

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

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

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

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

CW – Very positive. Novartis has had a collaboration with MMV for many years and on this project since 2016. We really benefit from the unique know-how and expertise of MMV in the field of malaria. It has helped us set up the study in a successful and scientifically sound way, fully meeting the needs of malaria physicians and patients.
**ESAC** Expert Scientific Advisory Committee

**GSB** Global Safety Board

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

**APM** Access & Product Management Committee

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**MMV-supported projects**

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**GOVERNANCE**

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**Target product profiles (TPPs)**

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

**Target candidate profiles (TCPs)**

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

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

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

ZY19489 (Zydus Lifesciences Ltd) + ferroquine

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

M5717 (Merck) + pyronaridine

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

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

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

The CANTAM study of over 8,500 malaria episodes across five African countries reported high effectiveness (a Day 28 PCR-adjusted cure rate of 98.6%) and safety and tolerability under conditions similar to everyday clinical practice in community settings. The study also proved that Pyramax works equally well in both male and female patients, with no difference in the rate of adverse events.

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

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

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

Pyramax - fast facts

- In 2012, Pyramax® (pyronaridine-artesunate), developed with Shin Poong, was granted a positive scientific opinion from the European Medicines Agency under Article 58 for the treatment of both P. falciparum and P. vivax uncomplicated malaria.
- A total of 2.2 million treatments of Pyramax have since been distributed, a third of which were in granule formulation for children.
- Both Pyramax tablet and granule formulations are cross-referenced on the WHO List of Prequalified Medicines and included in the WHO Model Lists of Essential Medicines for Adults and for Children.
- The adult tablets are approved in 29 countries and the paediatric granules in 19 countries, with further registrations ongoing.
Why was it important to study Pyramax as part of the CANTAM real-life study?

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

Why is Pyramax an important addition to the malaria toolbox?

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

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

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

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

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

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

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

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

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

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

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

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

Hydroxychloroquine/chloroquine stockpile donations in 2021

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

Monitoring global supply chain security

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

Bolstering support for African manufacturing of malaria medicines

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

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

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

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

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

**Modelling and simulation**
- Provided ongoing support to several other COVID-19 related research initiatives, including modelling and simulation platforms to predict:
  - potential drug-drug interactions between Ivermectin and ASAQ (in the DNDi-led ANTICOV study\(^1\))
  - drug concentrations in human lung epithelium for two antimalarials, amodiaquine and its active metabolite desethylamodiaquine, and pyronaridine

**Clinical development**
- Supported the progression into clinical development of ASAQ (in ANTICOV\(^1\) and the MMV-sponsored ReACT studies); and Pyramax\(^6\) (pyronaridine-artesunate) (in the ReACT study).
- Assembled an expert virology advisory board and provided technical advice to Shin Poong, that had completed Phase Ib trials of Pyramax to treat mild-to-moderate COVID-19 patients in Korea.

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\(^1\) ANTICOV: [https://dndi.org/research-development/portfolio/anticov](https://dndi.org/research-development/portfolio/anticov)

\(^6\) Pyramax: [https://www.mmv.org/pipeline/products/Pyramax](https://www.mmv.org/pipeline/products/Pyramax)
Placing the threat of relapse in its proper context

For a long time, *Plasmodium vivax* malaria was considered less severe than that caused by *Plasmodium falciparum*, and its clinical impact underestimated. However, this notion has changed, especially in terms of the impact on young children and pregnant women.1 Furthermore, *P. vivax* malaria is a particular challenge for elimination efforts due to the complex life cycle of the parasite. One infectious mosquito bite can cause both a blood-stage and liver-stage parasitic infection. If untreated, the liver-stage infection can lie dormant and then reactivate causing the patient to relapse repeatedly with new bouts of malaria. Transmission of the parasite is also driven largely by relapses from dormant liver stages.

Single-dose tafenoquine (*Krintafel/Kozenis*),2 developed by GSK and Medicines for MMV, represents a significant step forward, compared to the predominant standard of care (7-to-14-day primaquine regimens) for the treatment of the liver-stage infection to prevent *P. vivax* relapse. Expanding access to both treatments is crucial to prevent patient suffering and to eliminate the disease. However, their use in national malaria programmes remains a challenge. Even though both drugs are well tolerated by most people, in some individuals with lower levels of glucose-6-phosphate dehydrogenase (G6PD) – an enzyme that protects red blood cells from premature destruction – these drugs may cause serious haemolytic side effects. Testing for G6PD deficiency before prescribing this class of drug is therefore important for patient safety. New tools, including a quantitative, point-of-care G6PD test are becoming available and are starting to be used by several national malaria programmes.

In 2021, MMV and partner PATH, launched the Partnership for Vivax Elimination (PAVE) to accelerate the elimination of *P. vivax* malaria. Under this initiative, the first real-world study of a new *P. vivax* case management protocol with point-of-care G6PD testing before treatment with either single-dose tafenoquine or 7-day primaquine got underway in Brazil; plans are also in development to support additional real-world studies in Ethiopia, Indonesia, Papua New Guinea,3 Peru and Thailand.

Brazil: first real-world use of optimized radical cure with G6PD testing, primaquine and tafenoquine gets underway

In September 2021, the first real-world study of a new protocol for *P. vivax* case management known as Tafenoquine Roll-out STudy (TRuST) started in Brazil. The study is a collaboration between the Brazilian Ministry of Health and MMV, and is led by the Tropical Medicine Foundation of Amazonas and the Tropical Medicine Research Center of Rondônia. The first phase of the pilot study started in nine higher and medium-level healthcare facilities in the municipalities of Porto Velho and Manaus within the Amazonia region. It is estimated that around 5% of the population living in the Amazonia region have G6PD deficiency.4 Thus, health workers are fully trained in the new treatment algorithm and accurate use of the new tools. The first interim analysis assessed data from 600 patients attended to in these municipalities and concluded that patients were appropriately treated with the new drug tafenoquine based on the results of the G6PD test. In February 2022, the new treatment algorithm was rolled out at lower-level health facilities in these municipalities, expanding the study. The results of this study are expected by the end of 2022 and will help inform the Brazilian government’s decision whether to incorporate tafenoquine and the G6PD test into the national health system for patients over 16 years of age.

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2 Tafenoquine is marketed as *Kozenis* in Australia and *Krintafel* in the USA. Trademarks are owned by or licensed to the GSK group of companies.
3 Studies in Ethiopia, Indonesia, Papua New Guinea and Peru are supported with funding from Unitaid.
Representatives of the Brazilian Ministry of Health and Dr Dhelio Pereira, Director of Clinical Research at the Tropical Medicine Research Center of Rondonia (CEPEM) discuss the results of Phase I of TRuST and the next steps.

What has Phase I of TRuST revealed so far?

**Dhelio Pereira** – Introduction of the G6PD test brought greater safety not only for the use of tafenoquine, but also for choosing the appropriate therapeutic regimen of primaquine. The few cases that resulted in haemolysis in this period were caused by inappropriate use of primaquine for patients with intermediate or low G6PD activity.

**Ministry of Health** – The first phase of the study indicated that in medium and higher-level units, tafenoquine was used appropriately in more than 95% of cases, although there were challenges for local health services in organizing the training of professionals and monitoring of patients who had used the drug.

What are the next steps in this study?

**DP** – The results of the first phase were presented to the Independent Study Oversight Committee, which advised the Ministry of Health, MMV and the researchers to expand the study to the second phase. The new tools were introduced at lower-level health facilities including those in rural areas following training on the G6PD test and new treatment algorithm. Now all malaria diagnostic sites in the municipalities of Manaus and Porto Velho offer G6PD testing and tafenoquine.

How will the evidence generated be used?

**MOH** – The study will provide data on the implementation of tafenoquine in these two municipalities. A second study being carried out alongside TRuST, known as QualiTRuST, will provide findings on the perception of health professionals and patients. The Ministry of Health will bring this together with an evaluation of the process made at the local level, an evaluation by specialists, a cost-effectiveness and budget-impact analysis and a pharmacovigilance assessment to form a submission to the National Commission on Health Technologies (CONITEC). CONITEC will then make an assessment as to whether to incorporate tafenoquine and the G6PD test into the national health system, or Sistema Único de Saúde (SUS), for patients over 16 years of age.

**DP** – The evidence generated will help us better understand the challenges of implementing tafenoquine in the public health service and its acceptance by health workers and the population, as well as evaluate the costs and logistics of material distribution and data collection in the Amazonia region. This information will also be invaluable to other countries that are looking at whether to implement the G6PD test and tafenoquine.

How can tafenoquine support the country’s efforts to eliminate malaria (transmission, adherence, preventing relapse)?

**MOH** – The ability to treat hypnozoites and gametocytes in a single dose promotes better treatment adherence and, consequently, will help to reduce the transmission of *P. vivax* malaria. Furthermore, although there is no significant difference between the efficacy of tafenoquine and primaquine (a drug used for decades in Brazil), better adherence may also lead to a lower percentage of relapses in patients over 16 years of age with normal G6PD activity.

Is adherence to a 7-day treatment a challenge?

**DP** – In regions where the number of cases of *P. vivax* malaria is decreasing, knowledge about the disease also decreases and the importance of completing primaquine treatment is no longer valued, reducing adherence.

Which specific strategies are needed to improve adherence of primaquine within affected communities?

**MOH** – Health education actions with better targeting and accessible language for the affected populations, as well as the follow-up of treatment in locations with a lower level of transmission will be crucially important to ensure all patients understand the importance of completing the prescribed 7-day treatment regimen. To support this, we need operational capacity.

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

**DP** – I have been lucky enough to work with various teams within MMV, working on pre-clinical drug and compound development, diagnostic support, transmission blocking drug development and clinical trials, and now, on the implementation of two products, tafenoquine and the G6PD test. Everyone at MMV is a model of dedication, technical quality and love for what they do. Being in a malaria transmission region and being able to bring cutting-edge solutions to the local population in collaboration with MMV makes me proud and inspired to work harder and better.
New tools for malaria R&D: fast-tracking innovation for case management

Identifying resistance potential and assessing risks early in R&D

For medicines targeting infections, there is a risk that the pathogen will develop resistance, which may lead initially to infections which require a higher dose of medicine to treat, and ultimately the failure of the drug. This is true for many malaria medicines: over the years, the use of chloroquine, mefloquine and amodiaquine monotherapies eventually led to resistance, and their withdrawal in many countries.

Artemisinin combination therapies were designed to reduce the risk of resistance arising to any one drug. However, in 2008, patients with increased parasite clearance times were detected in Western Cambodia.\(^1\) The mutations in the parasite causing this shift were found to be concentrated in the Kelch 13\(^2\) gene. Artemisinin-based combination therapies (ACTs) were shown to be still active, provided there was no partner drug resistance.

New Kelch 13 mutations have now been reported in Africa, some of which are similar to those mutations reported in Asia. There have also been reports of delayed parasite clearance times. On the positive side, ACTs are still reported as being effective in treating malaria patients in Africa, provided there is no resistance to the partner drug.

Fortunately, to date no resistance has been reported in patients or in vitro to lumefantrine or pyronaridine. However, to counter this growing resistance risk, it is vital that researchers discover and develop antimalarial compounds with new mechanisms of action and high barriers to resistance. The risk with any compound where resistance can be easily selected is that they will fail early after launch, as illustrated by sulfadoxine-pyrimethamine, which failed as a treatment within a year of launch due to resistance.

Fortunately, as mentioned in chapter 4 (p. 18), MMV has traditionally focused on compounds which showed little propensity for resistance — and we are increasing our focus on this type of molecule. So, the hunt is on to discover and develop ‘irresistible’ compounds, where resistance cannot be selected either \textit{in vitro} (when tested against a billion parasites) and where no resistance is seen in early clinical studies.

Innovative drug research programmes are carefully designed and strive to progress compounds with promising properties that do not present an unmanageable susceptibility to select for resistance. To identify and prioritize these compounds is a perpetual challenge. A full and early understanding of both a drug candidate’s propensity to select for resistance and the possibility that this could translate into the drug’s clinical failure down the line is imperative. This assessment of the parasite’s genome and a drug’s sensitivity (in both cases to a specific compound) immediately gives comprehensive information on whether drug resistance is a significant risk for the future and, thus, which partner drugs would be most suitable within a combination.
**MMV’s new predictive strategy to identify potential resistance risks**

In May 2021, MMV published a new strategy illustrating a cost-effective approach for identifying and quantifying the risk of resistance in malaria drug discovery and drug development. This approach, with tests standardized across all projects, helps to characterize the resistance risk of candidate drugs and identify the optimum combination strategy to further reduce the potential of drug resistance to develop in the clinic.

**The guiding principle was to develop an assessment tool that could integrate data from across different parasitology platforms and studies to help predict the intrinsic risk of resistance emerging in patients, if not properly managed, and most importantly, its potential impact on clinical efficacy.**

The predictive tool was the outcome of a discovery project, led by Prof. David Fidock at Columbia University, USA, that focused on profiling potential new antimalarials in the laboratory to determine their propensity to select for resistance and characterizing such resistance to ascertain their suitability for further R&D. The project was awarded MMV’s Project of the Year 2020.

The impact of this project on MMV’s portfolio has been significant. This approach, including the use of genetic and genomic studies, has enhanced the understanding of resistance mechanisms and this information has, in turn, helped elucidate drug modes of action. As a consequence, over the past 11 years, the team has profiled over 215 compounds from MMV and partners and contributed to the discovery of over 20 new modes of action and resistance.

**Guided by the ‘triangle of resistance’**

The predictive tool relies on three pillars: the clinical outcome of resistance to the drug (successful treatment vs therapeutic failure), the genotyping of the recrudescent parasites, and the in vitro study of their sensitivity to the drug. This helps to build an understanding of the factors leading to clinical failure and, specifically, whether such failure is due to resistance or other factors, such as insufficient drug exposure. Verification of this triangle is vital before concluding that a clinical trial failure is due to resistance.

**Advantages of a predictive tool**

An early understanding of how candidate compounds lose efficacy as parasites evolve resistance will help the prioritization of candidate drugs and future drug targets, inform the necessary combination strategy, improve resistance detection in the field, and potentially help future drug design. If the analysis shows a significant and unacceptable risk of resistance this will allow early decisions to stop or deprioritize a compound/series.

The tool also presents a major advantage in terms of optimizing resources and accelerating research, with a focus on prioritizing the development of compounds that demonstrate a low risk of resistance generation and spread.

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**Lead author of the publication,**
**Dr Didier Leroy,**
Senior Director Drug Discovery, MMV.
Malaria Libre: open collaborative science to accelerate drug discovery

With the launch of MMV Open with our partners in 2010, MMV initiated a further evolution in malaria research through sharing data in the public domain. Over 200 groups benefited from the first iteration of MMV Open through the receipt of the Malaria Box that provided access to a set of compounds that drove the development of new medicines for malaria and other infectious diseases, resulting in new drug discovery projects and ideas. By opening the door to global research collaboration, MMV is making access to compounds and research tools more equitable, and transforming innovation.

Malaria Libre, a more recent project under the umbrella of MMV Open’s collaborative drug discovery, enables participants to share the structures of any molecules being made, as well as the results in biological assays. Anyone can contribute their ideas, time and resources, resulting in virtual team building for drug discovery projects. Malaria Libre can be compared to open-source software development, but for drug discovery.

Malaria Libre’s scientific activities take place in the participants’ laboratories, and results are shared in open forum discussions and meetings. The in-kind and intellectual contributions of researchers from around the globe include synthesizing compounds or running biological assays to discover preclinical candidates for malaria treatment and prevention.

Based in India, where malaria is endemic, Malaria Libre is a prime example of how excellent research groups working in different geographies without any legally binding agreement are able to contribute to real-time collaborative research, with the goal of identifying the first-ever preclinical candidate for malaria from an open-source project. The programme not only engages participants in a live global drug discovery project but also provides a platform to contribute ideas and share analyses in transparent discussions led by MMV scientists under the guidance of MMV’s Expert Scientific Committee. This project also provides opportunities for development and mentoring, especially for next-generation drug discovery scientists in malaria-endemic countries.

4 Participants include CSIR-Central Drug Research Institute, the Special Centre for Molecular Medicine at Jawaharlal Nehru University, and TCD Lifesciences in India, as well as research organizations from Australia, Brazil, South Africa, Uruguay and USA: Monash University, University of São Paulo, University of Stellenbosch, Universidad de la República | Montevideo, Massachusetts College of Pharmacy and Health Sciences, and Drexel University that have contributed with lab work.
**Why are MMV Open and Malaria Libre considered pioneering approaches to drug discovery?**

Open collaboration in research, especially drug discovery, is relatively rare. The advantages are many: researchers collaborating from diverse fields can bring in skills, expertise and facilities, adding immense value to the project. It saves us from re-inventing the wheel – for example, it is quite possible that an issue faced in the project has already been addressed and solved by other researchers and their learning can be immediately shared and implemented, thus saving time and resources.

**What is your role within MMV Open/Malaria Libre?**

I am a PhD medicinal chemist with over 20 years of experience, and joined MMV in 2018 to work on MMV Open. I am responsible for building research networks for malaria, particularly in the context of testing MMV compounds such as Open Access Boxes on non-malaria pathogens for other infectious diseases. I am currently leading the Malaria Libre project, helping to build both the scientific body of knowledge on malaria drug discovery as well as a strong open science community.

**How does the open science of Malaria Libre fulfil its aim?**

The primary aim is to identify a preclinical candidate. In parallel, we are working to build a strong community of next-generation drug discovery scientists committed to collaboration and open sharing of ideas and data. This open approach helps save time and resources. For example, based on the mode of action of a frontrunner compound confirmed by groups at Monash University, Drexel University and Jawaharlal Nehru University (JNU), the team decided to defer medicinal chemistry work on a series until more parasitology data was generated, especially on the propensity to generate resistance that would enable a decision to stop or go ahead with the series.

**What has Malaria Libre achieved so far and when could it deliver a preclinical candidate to advance into antimalarial research?**

Malaria Libre is still at an early hit-to-lead stage, where the hits identified from phenotypic screening are being optimized to identify promising lead compounds. So far, we have been able to build a network of collaborators who have proactively contributed to the project, despite a huge shift towards COVID-19 research. We hope to be able to deliver on our primary goal of a preclinical candidate by 2025, if all goes according to plan, but this is an experiment in a new way of working, so that’s quite an ambitious goal.

**Malaria Libre is operating out of India and working with several partners across the world – what do they contribute to the project?**

India is an important geography for drug research – its drug discovery work boasts a highly competent research community, robust infrastructure and skilled human resources. In India, Malaria Libre launched with the participation of researchers from three institutions: CSIR-Central Drug Research Institute to help synthesize compounds, the Special Centre for Molecular Medicine at JNU to conduct parasitology tests, and TCG Lifesciences to conduct the majority of compound screening, primary assays and syntheses. TCG is also engaged in chemistry work for other MMV projects. Other groups at Monash, Drexel and University of São Paulo have contributed to target deconvolution of the hits that are worked upon and other groups have supported medicinal chemistry. These have been made as in-kind contributions. The project team also has access to all the assay platforms that support the project progression.

**Does MMV have experience in empowering drug discovery research in other disease areas?**

The compound licensed out to Merck from Salvensis⁵ for preclinical development against schistosomiasis had its origin in one of the MMV Open libraries. In addition, hit compounds identified through screening of open-access compound collections are taken through iterative ‘make-test-analyse’ cycles that design drug candidates for other neglected diseases, like tuberculosis and Chagas.

**What’s next for MMV Open?**

We are anticipating the launch of the Global Health Priority Box (GHPB) in the second half of 2022 in collaboration with the Innovative Vector Control Consortium and Bristol Myers Squibb. Like the previous Open Access Boxes, the GHPB will comprise compounds that have shown promise against malaria or other neglected diseases or for vector control. It will be available free of charge to researchers with the only stipulation that their research is posted in the public domain. Meanwhile, we remain focused on identifying a high-quality preclinical candidate by 2025.
Raising the bar for all future preclinical candidates

MMV’s Project of the Year 2021 is awarded to a discovery team led by Dr Laura Sanz at GSK and Dr Stephen Brand at MMV, for the discovery of GSK4024484 (GSK484), a compound with potential for treatment of patients with uncomplicated malaria. MMV’s independent Expert Scientific Advisory Committee (ESAC) recommended GSK484 for this award owing to its high quality, including its fast and potent antimalarial activity against drug sensitive and resistant strains and ‘irresistibility’ i.e., no detectable resistance selection in vitro\(^1\), which makes it a potentially important public health tool as part of a future combination to drive the treatment, control and eradication of malaria.

New antimalarial therapeutics are needed to ensure that malaria cases can continue to be treated effectively, as emerging parasite resistance to frontline chemotherapies threatens control programmes in Africa\(^2\). GSK484, is a novel chemotype which exhibits rapid parasite clearance in vitro\(^3\) and in vivo\(^3\), and is predicted to have a low dose, when used clinically. This exciting molecule represents a novel structural series, with a mechanism of resistance different to current antimalarials in clinical use and no cross resistance with any compound in the MMV portfolio.

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1 A laboratory process that is not conducted in a living organism.
3 Studies in which the effects of various biological entities are tested on whole, living organisms or cells, usually animals, including humans, and plants, as opposed to a tissue extract or dead organism.
**Dr Laura Maria Sanz-Alonso**, Malaria Portfolio Leader, GSK fellow, GSK Global Health Medicines R&D Tres Cantos, Spain and **Dr Stephen Brand**, Associate Director, Drug Discovery, MMV, discuss the antimalarial preclinical candidate project.

**What are the attributes of GSK484 that make it a promising antimalarial candidate?**

**Laura Maria Sanz-Alonso** – Given the compound’s non-clinical safety profile – demonstrated by a toxicology programme, including selectivity profiles and evaluation of safety pharmacology, genetic toxicology, general toxicology and even developmental toxicity – it has the potential to be considered as a treatment for pregnant women.

**Stephen Brand** – Because the compound is fast acting, it has the potential to rapidly alleviate malaria symptoms. It is also potent, has a long-predicted half-life in humans and good drug-like properties – these factors combined suggest a very low dose will be required without an expensive complex formulation. The low risk of generating antimalarial resistance and potential for low cost of manufacture further make GSK484 an attractive partner for combination.

**Could you briefly describe the project: How did it begin and evolve?**

**LS** – GSK484 belongs to a chemical series, called the pyrazines, which were originally identified by GSK from a *P. falciparum* intraerythrocytic whole cell phenotypic screening⁴ conducted in 2010. The many hits⁵ from that screen were published as a Tres Cantos Antimalarial Set (TCAMS)⁶ and were the origin of numerous antimalarial programmes both at GSK and externally, particularly in a collaboration between MMV, GSK and Ferrer. Among the different chemical series identified, the promising early properties of the pyrazine hits and their structural novelty led us to prioritize them for a lead optimization programme that ultimately led to the identification of GSK484.

**SB** – GSK Tres Cantos in Madrid performed a screening of a large collection of GSK compounds against the parasite and identified thousands of hit compounds with good potency against the parasite. From that point, GSK worked on multiple chemical series aiming to improve the many characteristics required to turn them into effective treatments. One of these series, the pyrazines, was particularly interesting because of its irresistibility. After several years of work to improve the key properties, we were able to identify GSK484. The compound was approved in 2021 as a candidate by MMV and our ESAC and is now undergoing preclinical testing before human clinical studies can start.

**What key challenges did you face during this project?**

**LS** – The pyrazine series delivered a previous candidate molecule. However, despite its excellent parasitological profile, the previous compound was stopped because of concerns about potential risk of a human anaphylactoid reaction.⁷

**SB** – Given the termination of the previous pyrazine candidate, the most significant challenge was to understand the biological mechanism of the safety finding and to apply that knowledge to identify improved compounds without the risk; the team did an outstanding job in solving this, which gives us confidence in progressing GSK484 into pre-clinical and clinical development.

**How did collaboration with MMV contribute to the success of the project?**

**LS** – The collaboration between GSK and MMV has been key in identifying this new antimalarial opportunity. The work conducted by both parties as a team, along with MMV’s confidence in the potential of the series and our ability to address the safety risk, enabled us to initiate the back-up project that fortunately led to the identification of GSK484.

**How has team collaboration with GSK contributed to the success of the project?**

**SB** – If it weren’t for GSK’s commitment to global health and Laura and her team’s capability in malaria research, we wouldn’t have this candidate. They selected the starting points from their collection, performed the lead optimization and demonstrated tremendous leadership with their early safety studies which allowed them to successfully navigate the real challenges and deliver GSK484.

**What has been the impact of this project on MMV’s portfolio and drug discovery process?**

**SB** – This project adds another treatment option to our ever-strengthening portfolio, further increasing the probability of delivering single dose treatments which could ultimately replace artemisinin and other fast-acting drugs. I also believe that this compound is raising the bar for all future preclinical candidates because it has such a strong profile. Ideally, any compound that comes through in the future as a potential candidate effectively needs to be as good as GSK484, if not better.

**How does the project fit into MMV’s overarching strategy on resistance risk and improving malaria treatment during pregnancy?**

**SB** – In terms of pregnancy, GSK has already done some preclinical profiling on the compound which suggests that it could be a medicine which is safe during human pregnancies. The compound is also active against parasite strains that are resistant to current antimalarials, and it also appears to be very challenging for the parasite to develop resistance to this compound. It is important to say that these are still early days, and a lot more testing needs to be done, both in preclinical and in clinical development to prove that, but the first signs are promising.
Legal status
MMV is a Swiss foundation, established as a not-for-profit legal entity, registered in Geneva under statutes dated 15 November 1999. The summary 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 summary consolidated financial statements).

Revenue
Total revenue in 2021 amounted to USD 84.1 million. Every contribution over the years has helped to advance our mission and the ultimate goal of defeating malaria together.

MMV is highly grateful for these and previous commitments from all its donors and partners.

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**Figure 1: Total donations received in 2021**

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<th>Category</th>
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<td><strong>MMV total donation revenue 2021</strong></td>
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Expenditure

Total expenditure in 2021 amounted to USD 78.9 million. Research & development (R&D) expenditure amounted to USD 50.5 million. Access & product management (APM) expenditure amounted to USD 14.8 million. Other portfolio expenditure accounted to USD 0.5 million.

In 2021, corporate affairs, administration & finance and board expenditure amounted to USD 13.2 million.

Figure 2: MMV expenditure 2021
Total: USD 78.9 million

R&D & APM
Research & development 64%
Access & product management 19%
Other portfolio expenditure 1%

Indirect costs
Administration & finance 9%
Corporate affairs 7%

Programmatic spend per disease
MMV advanced its vast portfolio, addressing R&D gaps affecting low-resource settings while engaging in COVID-19-related activities.

Figure 3: Programmatic spend per disease
Total USD 45.3 million
Independent Auditor Report to the Management on the Summary Consolidated Financial Statements of MMV MEDICINES FOR MALARIA VENTURE, Meyrin

The accompanying summary consolidated financial statements, which comprise the summary consolidated statement of financial position as at 31 December 2021, summary consolidated statement of operations, summary consolidated statement of changes in capital and summary consolidated statement of cash flow for the period ended and related notes, are derived from the audited financial statements of MMV MEDICINES FOR MALARIA VENTURE for the year ended 31 December 2021. We expressed an unmodified audit opinion on those financial statements in our report dated 14 April 2022. Those financial statements, and the summary financial statements, do not reflect the effects of events that occurred subsequent to the date of our report on those financial statements.

The summary financial statements do not contain all the disclosures required by Swiss GAAP FER and Swiss law. Reading the summary financial statements, therefore, is not a substitute for reading the audited financial statements of MMV MEDICINES FOR MALARIA VENTURE.

Management's Responsibility for the Summary Financial Statements
Management is responsible for the preparation of a summary of the audited financial statements in accordance with Swiss GAAP FER and the requirements of Swiss law.

Auditor's Responsibility
Our responsibility is to express an opinion on the summary financial statements based on our procedures, which were conducted in accordance with Swiss Auditing Standard (SAS) 810, Engagement to Report on Summary Financial Statements.

Opinion
In our opinion, the summary financial statements derived from the audited financial statements of MMV MEDICINES FOR MALARIA VENTURE for the year ended 31 December 2021 are consistent, in all material respects, with those financial statements, in accordance with Swiss GAAP FER and Swiss law.

KPMG SA

Pierre-Henri Pingan
Licensed Audit Expert

Delphine Bourassa Anderson
Licensed Audit Expert

Geneva, 14 June 2022

Enclosure:
- Summary consolidated financial statements (summary consolidated statement of financial position as at 31 December 2021, summary consolidated statement of operations, summary consolidated statement of changes in capital and summary consolidated statement of cash flow for the period ended and related notes)
## MMV SUMMARY CONSOLIDATED STATEMENT OF FINANCIAL POSITION

### ASSETS

<table>
<thead>
<tr>
<th>Notes</th>
<th>31 Dec 2021 USD</th>
<th>31 Dec 2020 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cash and cash equivalents</strong></td>
<td>3</td>
<td>35,376,192</td>
</tr>
<tr>
<td><strong>Donations receivable</strong></td>
<td>7</td>
<td>4,954,481</td>
</tr>
<tr>
<td><strong>Accounts receivable</strong></td>
<td>8</td>
<td>8,869,203</td>
</tr>
<tr>
<td><strong>Tax receivable</strong></td>
<td>-</td>
<td>8,974</td>
</tr>
<tr>
<td><strong>Prepads</strong></td>
<td>-</td>
<td>644,143</td>
</tr>
<tr>
<td><strong>Prepaid portfolio commitments</strong></td>
<td>11</td>
<td>6,696,570</td>
</tr>
<tr>
<td><strong>Total current assets</strong></td>
<td>-</td>
<td>56,549,563</td>
</tr>
<tr>
<td><strong>Long-term assets</strong></td>
<td>-</td>
<td>24,278,093</td>
</tr>
<tr>
<td><strong>Total long-term assets</strong></td>
<td>-</td>
<td>80,827,656</td>
</tr>
<tr>
<td><strong>Total assets</strong></td>
<td>-</td>
<td>80,827,656</td>
</tr>
</tbody>
</table>

### LIABILITIES, CAPITAL & RESERVES

<table>
<thead>
<tr>
<th>Notes</th>
<th>31 Dec 2020 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accrued portfolio commitments</strong></td>
<td>7,169,406</td>
</tr>
<tr>
<td><strong>Deferred revenue</strong></td>
<td>9</td>
</tr>
<tr>
<td><strong>Other creditors</strong></td>
<td>1,234,129</td>
</tr>
<tr>
<td><strong>Accrued expenses</strong></td>
<td>2,657,891</td>
</tr>
<tr>
<td><strong>Short-term provisions</strong></td>
<td>6,135,606</td>
</tr>
<tr>
<td><strong>Foreign exchange contracts</strong></td>
<td>13,880,663</td>
</tr>
<tr>
<td><strong>Total current liabilities</strong></td>
<td>-</td>
</tr>
<tr>
<td><strong>Restricted operating funds</strong></td>
<td>16,511,914</td>
</tr>
<tr>
<td><strong>Restricted funds</strong></td>
<td>-</td>
</tr>
<tr>
<td><strong>Unrestricted funds</strong></td>
<td>-</td>
</tr>
</tbody>
</table>

### MMV SUMMARY CONSOLIDATED STATEMENT OF CHANGES IN CAPITAL

<table>
<thead>
<tr>
<th>Balance at 1 January 2021</th>
<th>Balance at 31 December 2020</th>
<th>Internal funds transfers</th>
<th>Gain/(loss) for the period</th>
<th>Balance at 31 December 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Restricted operating funds</strong></td>
<td>1,506,750</td>
<td>-29,143,260</td>
<td>15,430,081</td>
<td>16,936,831</td>
</tr>
<tr>
<td><strong>TOTAL RESTRICTED OPERATIONS FUNDS</strong></td>
<td>1,506,750</td>
<td>-29,143,260</td>
<td>15,430,081</td>
<td>16,936,831</td>
</tr>
<tr>
<td><strong>Paid-in capital</strong></td>
<td>4,000,000</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Foundation Fund</strong></td>
<td>29,998,911</td>
<td>-</td>
<td>1,806,167</td>
<td>(47,054)</td>
</tr>
<tr>
<td><strong>Unrestricted operating funds</strong></td>
<td>25,352,131</td>
<td>1,420,653</td>
<td>58,567,149</td>
<td>(74,558,597)</td>
</tr>
<tr>
<td><strong>TOTAL UNRESTRICTED FUNDS</strong></td>
<td>59,351,042</td>
<td>1,420,653</td>
<td>60,373,316</td>
<td>(74,605,651)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>60,857,792</td>
<td>1,420,653</td>
<td>89,516,576</td>
<td>(88,318,830)</td>
</tr>
</tbody>
</table>

The internal funds transfers between restricted and unrestricted funds in fiscal year 2021 concern allocation of 2020 expenditures (originally covered by an unrestricted grant) to a restricted grant based on donor’s request.
## MMV SUMMARY CONSOLIDATED STATEMENT OF OPERATIONS FOR THE PERIOD ENDED

### REVENUE

<table>
<thead>
<tr>
<th>Notes</th>
<th>31 Dec 2021 USD</th>
<th>31 Dec 2020 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donation revenue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restricted donations</td>
<td>7</td>
<td>27,948,645</td>
</tr>
<tr>
<td>Unrestricted donations</td>
<td>7</td>
<td>56,128,804</td>
</tr>
<tr>
<td>Total donations revenue</td>
<td>7</td>
<td>84,077,449</td>
</tr>
<tr>
<td>Restricted revenue from partnerships</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Unrestricted revenue from partnerships</td>
<td>932,622</td>
<td>1,362,337</td>
</tr>
<tr>
<td>Other unrestricted revenue</td>
<td>133,897</td>
<td>164,603</td>
</tr>
<tr>
<td>Total other revenue</td>
<td></td>
<td>1,066,319</td>
</tr>
<tr>
<td>TOTAL REVENUE</td>
<td>8</td>
<td>85,143,768</td>
</tr>
</tbody>
</table>

### EXPENDITURE

<table>
<thead>
<tr>
<th>Notes</th>
<th>31 Dec 2021 USD</th>
<th>31 Dec 2020 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portfolio expenditure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discovery project expenditure</td>
<td>10</td>
<td>16,906,597</td>
</tr>
<tr>
<td>Translational project expenditure</td>
<td>10</td>
<td>18,761,946</td>
</tr>
<tr>
<td>Development project expenditure</td>
<td>10</td>
<td>14,757,047</td>
</tr>
<tr>
<td>Access &amp; product management project expenditure</td>
<td>10</td>
<td>14,774,878</td>
</tr>
<tr>
<td>Other portfolio expenditure</td>
<td>562,556</td>
<td>2,286,135</td>
</tr>
<tr>
<td>Total portfolio expenditure</td>
<td></td>
<td>65,763,024</td>
</tr>
<tr>
<td>Support of portfolio expenditure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Board meetings expenditure</td>
<td>16</td>
<td>57,426</td>
</tr>
<tr>
<td>Corporate affairs expenditure</td>
<td></td>
<td>5,690,513</td>
</tr>
<tr>
<td>Administration &amp; finance expenditure</td>
<td></td>
<td>7,424,540</td>
</tr>
<tr>
<td>Total support of portfolio expenditure</td>
<td></td>
<td>13,172,479</td>
</tr>
<tr>
<td>Other expenditure</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Funding reimbursements</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>TOTAL EXPENDITURE</td>
<td></td>
<td>78,935,503</td>
</tr>
</tbody>
</table>

### RESULT FROM OPERATING ACTIVITIES

<table>
<thead>
<tr>
<th>Notes</th>
<th>31 Dec 2021 USD</th>
<th>31 Dec 2020 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial Income</td>
<td>13</td>
<td>477,334</td>
</tr>
<tr>
<td>Financial Expenses</td>
<td>13</td>
<td>(2,069,233)</td>
</tr>
<tr>
<td>Net financial result</td>
<td></td>
<td>(1,591,899)</td>
</tr>
<tr>
<td>Of which are related to the Foundation Fund</td>
<td></td>
<td>66,167</td>
</tr>
</tbody>
</table>

### NET SURPLUS PRIOR TO ALLOCATIONS

<table>
<thead>
<tr>
<th>Notes</th>
<th>31 Dec 2021 USD</th>
<th>31 Dec 2020 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer (to) donor restricted operating funds</td>
<td>(439,025)</td>
<td>(15,430,081)</td>
</tr>
<tr>
<td>NET SURPLUS/(DEFICIT) PRIOR TO ALLOCATIONS TO UNRESTRICTED FUNDS</td>
<td>4,177,341</td>
<td>(14,232,334)</td>
</tr>
</tbody>
</table>

### ALLOCATIONS

<table>
<thead>
<tr>
<th>Notes</th>
<th>31 Dec 2021 USD</th>
<th>31 Dec 2020 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer (to) from unrestricted operating funds</td>
<td>(3,722,831)</td>
<td>15,991,448</td>
</tr>
<tr>
<td>Transfer (to) from Foundation Fund</td>
<td>(454,513)</td>
<td>(1,759,113)</td>
</tr>
</tbody>
</table>
## MMV SUMMARY CONSOLIDATED STATEMENT OF CASH FLOW FOR THE PERIOD ENDED

<table>
<thead>
<tr>
<th>Notes</th>
<th>2021</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>USD</td>
<td>USD</td>
</tr>
<tr>
<td><strong>(LOSS)/SURPLUS FOR THE YEAR</strong></td>
<td>4,616,366</td>
<td>1,197,747</td>
</tr>
<tr>
<td><strong>CASH FLOW FROM OPERATING ACTIVITIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depreciation</td>
<td>4</td>
<td>81,924</td>
</tr>
<tr>
<td>(Increase)/decrease in donations receivable</td>
<td>(4,315,235)</td>
<td>(219,737)</td>
</tr>
<tr>
<td>(Increase)/decrease in accounts receivable</td>
<td>8</td>
<td>7,994,883</td>
</tr>
<tr>
<td>(Increase)/decrease in tax receivable</td>
<td>(1,522)</td>
<td>256,541</td>
</tr>
<tr>
<td>(Increase)/decrease in portfolio-related prepaid expenses</td>
<td>11</td>
<td>3,759,986</td>
</tr>
<tr>
<td>(Increase)/decrease in prepaid expenses</td>
<td>(87,961)</td>
<td>179,597</td>
</tr>
<tr>
<td>(Increase)/decrease in long-term receivable</td>
<td>8</td>
<td>7,921,620</td>
</tr>
<tr>
<td>Increase/(decrease) in accrued portfolio-related commitments</td>
<td>(6,109,428)</td>
<td>(1,311,093)</td>
</tr>
<tr>
<td>Increase/(decrease) in deferred revenue</td>
<td>9</td>
<td>(2,800,000)</td>
</tr>
<tr>
<td>Increase/(decrease) in other creditors</td>
<td>(1,090,309)</td>
<td>681,151</td>
</tr>
<tr>
<td>Increase/(decrease) in accrued expenses</td>
<td>(409,844)</td>
<td>304,919</td>
</tr>
<tr>
<td>Increase/(decrease) in provisions</td>
<td>6</td>
<td>(241,875)</td>
</tr>
<tr>
<td>Increase/(decrease) in reserves due to reimbursement of prior years expenditures</td>
<td>-</td>
<td>1,420,652</td>
</tr>
<tr>
<td>Unrealized foreign currency (gain)/loss</td>
<td>236,691</td>
<td>(616,062)</td>
</tr>
<tr>
<td>Unrealized (gain)/loss on investment portfolio - Foundation Fund</td>
<td>13</td>
<td>(399,589)</td>
</tr>
<tr>
<td>(Increase)/decrease in investment portfolio - Foundation Fund</td>
<td>5</td>
<td>333,422</td>
</tr>
<tr>
<td><strong>CASH FLOW RESULTING FROM OPERATING ACTIVITY</strong></td>
<td>(6,500,637)</td>
<td>(16,060,478)</td>
</tr>
<tr>
<td><strong>CASH FLOW FROM INVESTMENT ACTIVITY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Increase)/decrease in guarantees</td>
<td>8,583</td>
<td>(16,044)</td>
</tr>
<tr>
<td>(Increase)/decrease in foreign exchange contracts</td>
<td>29,113</td>
<td>58,950</td>
</tr>
<tr>
<td>(Increase)/decrease in fixed assets</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td><strong>CASH FLOW RESULTING FROM INVESTMENT ACTIVITY</strong></td>
<td>37,696</td>
<td>7,259</td>
</tr>
<tr>
<td><strong>NET INCREASE/(DECREASE) OF CASH AND CASH EQUIVALENTS</strong></td>
<td>(6,462,941)</td>
<td>(16,053,219)</td>
</tr>
<tr>
<td>Cash &amp; cash equivalents at beginning of year</td>
<td>41,857,848</td>
<td>57,233,655</td>
</tr>
<tr>
<td>Effect of exchange rate fluctuations on cash held</td>
<td>(18,715)</td>
<td>677,412</td>
</tr>
<tr>
<td>Cash &amp; cash equivalents at end of year</td>
<td>35,376,192</td>
<td>41,857,848</td>
</tr>
</tbody>
</table>
As all Swiss foundations, Medicines for Malaria Venture is monitored by the Swiss Federal Supervisory Board for Foundations. The summary consolidated financial statements for the year ended 31 December 2021 were approved for issue by the MMV Board on 13 April 2022.

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

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

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

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

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

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

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

These summary consolidated financial statements have been extracted from the full consolidated financial statements with the exception of:
  ➔ prior year information (note 4 and 7),
  ➔ portfolio expenditures table (note 10),
  ➔ salaries and related charges table (note 12),
  ➔ management compensation (note 16).

b) Foreign currency translation
The summary 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 in effect on the date of the transaction. Monetary assets and liabilities denominated in foreign currencies are translated at the foreign exchange rate in effect on the date of the balance sheet. Foreign exchange differences arising on translation are recognized in the summary consolidated statement of operations. Non-monetary assets and liabilities that are measured at historical cost in a foreign currency are translated using the exchange rate on the date of the transaction.

The following exchange rates were used at year end:

<table>
<thead>
<tr>
<th>Year</th>
<th>CHF 1</th>
<th>USD 1</th>
<th>EUR 1</th>
<th>GBP 1</th>
<th>AUD 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>2021</td>
<td>1.095356</td>
<td>1.134199</td>
<td>1.351043</td>
<td>0.726113</td>
<td></td>
</tr>
<tr>
<td>2020</td>
<td>1.133052</td>
<td>1.226373</td>
<td>1.364900</td>
<td>0.770745</td>
<td></td>
</tr>
<tr>
<td>2021</td>
<td>0.912945</td>
<td>0.881679</td>
<td>0.740169</td>
<td>1.377196</td>
<td></td>
</tr>
<tr>
<td>2020</td>
<td>0.882572</td>
<td>0.815413</td>
<td>0.732654</td>
<td>1.297446</td>
<td></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 summary consolidated financial statements.

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

Critical accounting judgements in applying MMV accounting policies pertain to:

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. When a donor has validated a report and associated expenditures, the associated donation is considered as a revenue of the year and as receivable as of year-end.

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>2021 USD</th>
<th>2020 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petty cash</td>
<td>7,065</td>
<td>6,475</td>
</tr>
<tr>
<td>Bank balances</td>
<td>27,831,094</td>
<td>33,689,235</td>
</tr>
<tr>
<td>Time deposits</td>
<td>7,538,033</td>
<td>8,162,138</td>
</tr>
<tr>
<td>Total cash and cash equivalents</td>
<td>35,376,192</td>
<td>41,857,848</td>
</tr>
</tbody>
</table>

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

The following depreciation rates are used depending on the fixed asset category:

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

<table>
<thead>
<tr>
<th></th>
<th>Fixtures &amp; installations USD</th>
<th>Office furniture USD</th>
<th>Computers &amp; equipment USD</th>
<th>Total USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2021 Costs at 1 January</td>
<td>1,039,637</td>
<td>392,363</td>
<td>302,346</td>
<td>1,734,345</td>
</tr>
<tr>
<td>Additions</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Disposals</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>At 31 December</td>
<td>1,039,637</td>
<td>392,363</td>
<td>302,346</td>
<td>1,734,345</td>
</tr>
<tr>
<td>Accumulated depreciation at 1 January</td>
<td>876,315</td>
<td>390,886</td>
<td>259,077</td>
<td>1,526,278</td>
</tr>
<tr>
<td>Charge for the year</td>
<td>52,080</td>
<td>1,079</td>
<td>28,765</td>
<td>81,924</td>
</tr>
<tr>
<td>Disposals</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>At 31 December</td>
<td>928,395</td>
<td>391,965</td>
<td>287,842</td>
<td>1,608,202</td>
</tr>
<tr>
<td>Net book value at 31 December</td>
<td>111,242</td>
<td>398</td>
<td>14,504</td>
<td>126,143</td>
</tr>
</tbody>
</table>

5. INVESTMENT PORTFOLIO – FOUNDATION FUND
In 2019, the MMV Board of Directors approved the establishment of a directly controlled quasi-endowment structure (the Foundation Fund) to invest the revenues from the GSK Krintafel (tafenoquine) partnership described in Note 8 below, as well as any possible and similar future extraordinary revenue. The long-term strategic objective of the Foundation Fund is to improve the conditions for MMV business sustainability, and/or to pursue possible future opportunities, which are consistent with its humanitarian mission, but may be restricted by the current business model of the foundation. In 2019, the Board also approved the related investment policy and appointed an investment manager for the Foundation Fund, following a competitive selection process, and approved the transfer to the investment manager of the initial 50% received from GSK (described in Note 8). The investment is classified as a long-term asset, as the intention of MMV is to keep these investments in the foreseeable future. In compliance with the investment policy approved by the Board, the above-mentioned assets were invested in:

- a discretionary fixed interest portfolio (USD-denominated, investment-grade bonds, 87.5% of total at inception, 84% as of Dec 31, 2021);
- a well-known exchange-traded fund, or ETF, (the MSCI World ESG Index) reflecting the performance of the global equity markets (10% of total at inception, 14% as of Dec 31, 2021); and
- a money market fund (2.5% of total at inception, 2% as of Dec 31, 2021).

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

<table>
<thead>
<tr>
<th></th>
<th>2021 USD</th>
<th>2020 USD</th>
<th>2021 performance USD</th>
<th>2020 performance USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Money market funds</td>
<td>356,019</td>
<td>357,577</td>
<td>-0.44%</td>
<td>0.03%</td>
</tr>
<tr>
<td>MSCI World ESG index</td>
<td>2,132,820</td>
<td>1,737,825</td>
<td>22.73%</td>
<td>17.42%</td>
</tr>
<tr>
<td>Fixed interest portfolio (discretionary mandate)</td>
<td>13,103,746</td>
<td>13,431,016</td>
<td>-2.44%</td>
<td>6.65%</td>
</tr>
<tr>
<td>Total</td>
<td>15,592,585</td>
<td>15,526,418</td>
<td>0.43%</td>
<td>7.59%</td>
</tr>
</tbody>
</table>
6. SHORT-TERM PROVISIONS

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

<table>
<thead>
<tr>
<th></th>
<th>Unused vacation provision</th>
<th>Total provisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance at 1 January 2020</td>
<td>838 540</td>
<td>838 540</td>
</tr>
<tr>
<td>Use/release</td>
<td>(838 540)</td>
<td>(838 540)</td>
</tr>
<tr>
<td>Allocation for the year</td>
<td>1 377 481</td>
<td>1 377 481</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balance at 31 December 2020</td>
<td>1 377 481</td>
<td>1 377 481</td>
</tr>
<tr>
<td>Use/release</td>
<td>(1 377 481)</td>
<td>(1 377 481)</td>
</tr>
<tr>
<td>Allocation for the year</td>
<td>1 135 606</td>
<td>1 135 606</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balance at 31 December 2021</td>
<td>1 135 606</td>
<td>1 135 606</td>
</tr>
</tbody>
</table>

7. REVENUE AND DONATIONS RECEIVABLE

Revenue recognition

Unrestricted grants

An unrestricted grant is recognized as revenue in the summary 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 15.

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

Restricted grants

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

Deferred revenue

When a grant associated to a specific project is paid to MMV prior to the start of this project, this revenue is considered as deferred and will be recognized only during the fiscal year in which the project starts.

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.

Summary of donations received or committed during 2021:

<table>
<thead>
<tr>
<th>Description</th>
<th>Cash received 2021</th>
<th>Revenue recognized during previous year</th>
<th>Donations receivable</th>
<th>Revenue deferred from previous year</th>
<th>Revenue deferred to following year</th>
<th>Unrealized foreign exchange (gain)/loss</th>
<th>Total revenue as per statement of operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian Government Department of Foreign Affairs and Trade (DFAT)</td>
<td>2 745 116</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 745 116</td>
</tr>
<tr>
<td>Bill &amp; Melinda Gates Foundation (Core grant)</td>
<td>38 170 000</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>36 170 000</td>
</tr>
<tr>
<td>Individual donors</td>
<td>13 648</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13 648</td>
</tr>
<tr>
<td>Irish Government Department of Foreign Affairs and Trade (Irish Aid)</td>
<td>1 195 321</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 195 321</td>
</tr>
<tr>
<td>UK Foreign, Commonwealth &amp; Development Office (FCDO)</td>
<td>13 656 725</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13 656 725</td>
</tr>
<tr>
<td>Swiss Agency for Development and Cooperation (DEZA/SDC)</td>
<td>2 347 994</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 347 994</td>
</tr>
<tr>
<td>Total unrestricted donations</td>
<td>56 128 804</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>56 128 804</td>
</tr>
<tr>
<td>European and Developing Countries Clinical Trials Partnership (EDCTP, PCAM Africa grant)</td>
<td>-</td>
<td>-</td>
<td>1 145 690</td>
<td>-</td>
<td>-</td>
<td>6 666</td>
<td>1 152 356</td>
</tr>
<tr>
<td>European and Developing Countries Clinical Trials Partnership (EDCTP, Sinodo grant)</td>
<td>243 436</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>243 436</td>
</tr>
<tr>
<td>German Federal Ministry of Education and Research (BMBF)</td>
<td>3 317 409</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 317 409</td>
</tr>
<tr>
<td>Global Health Innovative Technology Fund (GHIT)</td>
<td>667 211 (154 905)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>822 116</td>
</tr>
<tr>
<td>Korea International Cooperation Agency (KOICA) Global Disease Eradication Fund (GDEF)</td>
<td>-</td>
<td>-</td>
<td>2 800 000</td>
<td>-</td>
<td>-</td>
<td>3 935</td>
<td>516 241</td>
</tr>
<tr>
<td>Netherlands Ministry of Foreign Affairs (DGIS)</td>
<td>4 321 722</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4 321 722</td>
</tr>
<tr>
<td>Principality of Monaco Direction de la Coopération Internationale (DCI)</td>
<td>121 701 (122 637)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>936</td>
</tr>
<tr>
<td>Program for Appropriate Technology in Health (PATH, VivaAccess grant)</td>
<td>722 413</td>
<td>-</td>
<td>248 692</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>971 105</td>
</tr>
<tr>
<td>Swiss Agency for Development and Cooperation (DEZA/SDC, Antimalarial Treatment Options for Pregnant Women)</td>
<td>433 859</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>433 859</td>
</tr>
<tr>
<td>UK Foreign, Commonwealth &amp; Development Office (FCDO, South Africa ReAct study)</td>
<td>3 053 038</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 053 038</td>
</tr>
<tr>
<td>UNITAID (Supply grant)</td>
<td>1 015 796</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 015 796</td>
</tr>
<tr>
<td>UNITAID (Vivaction Plan grant)</td>
<td>6 162 453</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6 162 453</td>
</tr>
<tr>
<td>United States Agency for International Development (USAID)</td>
<td>769 501 (368 369)</td>
<td>3 560 098</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 921 269</td>
</tr>
<tr>
<td>Total restricted donations</td>
<td>20 828 539 (645 911)</td>
<td>4 954 480</td>
<td>2 800 000</td>
<td>-</td>
<td>11 537</td>
<td>27 948 645</td>
<td></td>
</tr>
</tbody>
</table>

TOTAL DONATIONS

76 957 343 (645 911) 4 954 480 2 800 000 - 11 537 27 948 645

Of the total donations recognized in the summary consolidated statement of operations, USD 13,648 were received through MMV North America Inc.
agreed to reimburse 50% of MMV’s cumulative costs for the period from 2008 to 31 December 2018 in Q1 2019, 25% in July 2022 and the residual 25% in July 2023. The two latter payments are 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, amounted to USD 28,426,969. Therefore, MMV recognized this amount as revenue from the GSK partnership during fiscal year 2018. MMV also booked in its summary consolidated statement of financial position as of 31 December 2018, 50% of the above amount, i.e. USD 14,213,484, as a short-term account receivable due in March 2019; and USD 14,213,484 as a long-term account receivable (to account for two residual payments of USD 7,106,742 each, due in July 2022 and July 2023).

In March 2019 MMV received the first payment from GSK in full. In 2020 MMV incurred additional net expenditure of USD 664,021 (2019: USD 1,354,081) in the co-development of Krintafel. As the two parties had agreed that GSK would refund any additional expenditure incurred by MMV after 1 January 2019, by increasing the two residual payment amounts, MMV recognized USD 388,345 in 2021, USD 664,020 in 2020 and USD 1,354,081 in 2019 as revenue from the GSK partnership. MMV also increased the receivable by the same amount, so that the total of the two residual payments due in July 2022 and July 2023 increased to USD 16,619,932 (2020: USD 16,231,587). Therefore, MMV is due a first payment of USD 8,309,966 at the end of July 2022 and a second payment of USD 8,309,966 at the end of July 2023.

In 2021 and 2020, MMV also recognized another revenue for USD 385,900 and USD 264,378 respectively from GSK in respect of the co-development of co-development of the project GSK701 (or MMV 367).

Other

In 2021, in addition to the above-mentioned revenues from GSK, MMV booked the following revenues from partnerships: USD 91,500 (2020: USD 140,970) from Janssen in respect of the development of P218 and 1M-atovalaquine, and USD 66,878 (2020: USD 292,968) from Shin Poong.

MMV plans to use the above-mentioned revenues from partnerships in support of its charitable mission.
11. PREPAID PORTFOLIO COMMITMENTS

Prepaid portfolio commitments are payments made to grantees or suppliers for goods or services which will be only delivered during the next fiscal years.

As of 31 December 2021, there are the following major categories of prepayments in relation with MMV portfolio projects:

<table>
<thead>
<tr>
<th>Category</th>
<th>2021</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine prepayment</td>
<td>2,575,125</td>
<td>4,500,000</td>
</tr>
<tr>
<td>EDCTP Pamafica prepayments to subgrantees</td>
<td>2,850,763</td>
<td>4,199,643</td>
</tr>
<tr>
<td>Vivaction project prepayment</td>
<td>630,586</td>
<td>-</td>
</tr>
<tr>
<td>Product development related</td>
<td>206,249</td>
<td>662,163</td>
</tr>
<tr>
<td>Discovery related</td>
<td>148,755</td>
<td>453,167</td>
</tr>
<tr>
<td>Translational related</td>
<td>130,080</td>
<td>214,236</td>
</tr>
<tr>
<td>Access and Product Management related</td>
<td>101,810</td>
<td>561,395</td>
</tr>
<tr>
<td>Other prepaid portfolio commitments</td>
<td>55,202</td>
<td>55,942</td>
</tr>
<tr>
<td><strong>Total prepaid portfolio commitments</strong></td>
<td><strong>6,696,570</strong></td>
<td><strong>10,646,546</strong></td>
</tr>
</tbody>
</table>

The significant decrease in prepaid portfolio commitments is mainly due to the following items:

a) Use of a restricted donation of USD 4,984,000 received from the Bill & Melinda Gates Foundation in 2020 aimed at the procurement and distribution of 120 million tablets of Chloroquine Phosphate 250mg, with an expiry date of April 2023. Chloroquine is a generic oral medication initially used in the treatment and prevention of all malaria species (Plasmodium falciparum, P. vivax, P. ovale, and P. malariae). It is no longer used for P. falciparum, as there is widespread resistance to it and ACTs are now the standard of care, but it is still the main treatment against the blood stage of P. vivax malaria. This restricted grant from the Bill & Melinda Gates Foundation was accounted for as “revenue” in 2020. As pharmaceutical products to be donated in the context of MMV’s mission can only be accounted for as “expenditure” upon physical and legal transfer of ownership to the final beneficiaries (in the specific case, the Ministries of Health of India and Ethiopia and other similar entities), In 2020 MMV accounted for the entire stock of 120 million tablets as “prepaids”. In 2021 MMV transferred ownership of 50 million tablets to the Ethiopian Ministry of Health / Ethiopian Pharmaceuticals Supply Agency and book as “expenditure” the value of this part of the stock. As a result, the value of the “prepaid” commitment was reduced from USD 4,500,000 to USD 2,575,125. The residual value of the 70 million tablets will be booked as “expenditure” as soon as the organization will either partly or wholly transfer its ownership.

b) Use of a restricted donation from the European and Developing Countries Clinical Trials Partnership (EDCTP) as a pre-financing grant equivalent to USD 9,698,419, which was recognized as a revenue in fiscal year 2020. In 2020 MMV (as leader of the consortium) released advance payments to other consortium members for a total amount equivalent to USD 5,848,430 to cover the costs of activities supported by the EDCTP grant over the period 2020-21. As of December 31, 2020, the total amount of outstanding prepaid portfolio commitments related to 2021 activities funded by the EDCTP grant was equivalent to USD 2,850,763.

c) Use of a USD 6,131,253 restricted donation from Unitaid in respect of the VivAction project, which was recognized as a revenue in fiscal year 2021. In 2021 MMV (as leader of the consortium) released advance payments to other consortium members for a total amount equivalent to USD 1,303,178 to cover the costs of activities supported by the Unitaid grant. As a result, as of December 31, 2021, the outstanding prepaid portfolio commitment related to 2022 activities funded by the Unitaid grant was equivalent to USD 630,586.

12. PERSONNEL EXPENSES

Salaries and related charges were as follows:

<table>
<thead>
<tr>
<th>Category</th>
<th>2021</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capital ratio</td>
<td>117.0%</td>
<td>109.8%</td>
</tr>
<tr>
<td>Amount payable to pension fund</td>
<td>4,596</td>
<td>684</td>
</tr>
</tbody>
</table>

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

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

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

On August 24, 2021, MMV entered into twelve foreign exchange “forward” contracts with one of its banks to buy on twelve pre-fixed dates in 2022 (once every month) an amount of CHF 2,000,000 (total CHF 24m), and to sell on the same dates the equivalent USD-denominated amounts at pre-agreed USD CHF exchange rates (USD CHF range: 0.901 – 0.911, average 0.906). Such “forward” contracts are used for hedging purposes (as most of MMV’s revenues are USD-denominated and only a small portion are expressed in CHF, while a significant portion of its operating expenditure are CHF-denominated); they are recognized at fair value on the day when they are entered; and they are recorded as either receivables or liabilities.

<table>
<thead>
<tr>
<th>Financial income</th>
<th>2021 USD</th>
<th>2020 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrealized gain on portfolio investments</td>
<td>399,589</td>
<td>1,142,056</td>
</tr>
<tr>
<td>Bank interests</td>
<td>11,757</td>
<td>194,735</td>
</tr>
<tr>
<td>Exchange gain from CHF</td>
<td>-</td>
<td>626,178</td>
</tr>
<tr>
<td>Exchange gain from EUR</td>
<td>-</td>
<td>375,088</td>
</tr>
<tr>
<td>Exchange gain from AUD</td>
<td>-</td>
<td>182,083</td>
</tr>
<tr>
<td>Exchange gain from GBP</td>
<td>65,988</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>477,334</strong></td>
<td><strong>2,520,140</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Financial expenses</th>
<th>2021 USD</th>
<th>2020 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss on foreing exchange forward contracts</td>
<td>88,063</td>
<td>58,951</td>
</tr>
<tr>
<td>Bank charges</td>
<td>62,908</td>
<td>111,563</td>
</tr>
<tr>
<td>Exchange loss from GBP</td>
<td>-</td>
<td>280,668</td>
</tr>
<tr>
<td>Exchange loss from CHF</td>
<td>1,304,538</td>
<td>-</td>
</tr>
<tr>
<td>Exchange loss from EUR</td>
<td>327,612</td>
<td>-</td>
</tr>
<tr>
<td>Exchange loss from AUD</td>
<td>38,377</td>
<td>-</td>
</tr>
<tr>
<td>Exchange loss from JPY</td>
<td>8,528</td>
<td>-</td>
</tr>
<tr>
<td>Unrealized loss on money market deposit</td>
<td>239,207</td>
<td>67,604</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2,069,233</strong></td>
<td><strong>518,786</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Positive value</th>
<th>Negative value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign exchange forward contracts</td>
<td>Hedging</td>
<td>(88,063)</td>
</tr>
<tr>
<td>Total financial instruments</td>
<td>-</td>
<td>(88,063)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Financial income</th>
<th>2021 USD</th>
<th>2020 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrealized gain on portfolio investments</td>
<td>399,589</td>
<td>1,142,056</td>
</tr>
<tr>
<td>Bank interests</td>
<td>11,757</td>
<td>194,735</td>
</tr>
<tr>
<td>Exchange gain from CHF</td>
<td>-</td>
<td>626,178</td>
</tr>
<tr>
<td>Exchange gain from EUR</td>
<td>-</td>
<td>375,088</td>
</tr>
<tr>
<td>Exchange gain from AUD</td>
<td>-</td>
<td>182,083</td>
</tr>
<tr>
<td>Exchange gain from GBP</td>
<td>65,988</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>477,334</strong></td>
<td><strong>2,520,140</strong></td>
</tr>
</tbody>
</table>

14. LEASES

Non-cancellable operating lease rentals are payable as follows:

<table>
<thead>
<tr>
<th>Period</th>
<th>2021 USD</th>
<th>2020 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than one year</td>
<td>733,044</td>
<td>1,028,830</td>
</tr>
<tr>
<td>Between one and five years</td>
<td>76,359</td>
<td>2,732,081</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>809,403</strong></td>
<td><strong>3,760,911</strong></td>
</tr>
</tbody>
</table>

MMV has several operating leases. These leases generally run for a period of six years, with an option to renew the lease after that date. During the year ended 31 December 2021, USD 1,012,399 was recognized as an expense in the summary consolidated statement of operations in respect of operating leases (2020: USD 1,075,537).

In September 2017 MMV renewed the rental agreement in respect of its Geneva headquarters (approximately 1,850 m2) for the six-year period running from 1 September 2018 to 31 August 2024. In 2018 an amendment was signed with the landlord to increase the size of the MMV office to approximately 2,000 m2. Under the terms of the rental agreement, MMV can unilaterally terminate the lease every two years (with value date 31 August 2020, 31 August 2022, and 31 August 2024) with one-year notice (by 31 August 2019, 31 August 2021, and 31 August 2023 respectively). In consideration of the implementation of a new “hybrid” work model at MMV (which calls for increased balance between office and home-office flexibility) and the subsequent expected reduction in the size of the office space needed, in August 2021 MMV gave notice to the landlord for value date 31 August 2022, and initiated a negotiation on the future size of the office space and its rental costs.

15. 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>Period</th>
<th>2021 USD</th>
<th>2020 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than one year</td>
<td>78,827</td>
<td>73,957,503</td>
</tr>
<tr>
<td>Between one and five years</td>
<td>90,055,460</td>
<td>130,715,668</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>168,882,754</strong></td>
<td><strong>204,673,171</strong></td>
</tr>
</tbody>
</table>
16. RELATED PARTIES
MMV has related-party relationships 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>2021</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>USD</td>
<td>USD</td>
</tr>
<tr>
<td>Board members &amp; meetings</td>
<td>57,426</td>
<td>219,031</td>
</tr>
</tbody>
</table>

There were no loans to Directors or executive officers for the years ended 31 December 2021 and 31 December 2020.

Some donors are represented in the foundation council. MMV management considers that their presence on the foundation council does not affect the nature of the relationship between MMV and these donors. These donors are therefore not considered related parties. Therefore, all MMV donors have been considered third parties.

MMV runs an annual evaluation of identification of potential related parties, this is done at the Senior Management level and as well with Board members. The nature and volume of transactions with the identified related parties are summarized in the following table.

<table>
<thead>
<tr>
<th></th>
<th>Transactions during the year</th>
<th>Receivable/(payable) at year-end</th>
<th>Transactions during the year</th>
<th>Receivable/(payable) at year-end</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategic partnership</td>
<td>270,577</td>
<td>-</td>
<td>77,799</td>
<td>-</td>
</tr>
<tr>
<td>Schooling fees</td>
<td>84,373</td>
<td>-</td>
<td>128,665</td>
<td>16,639</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>354,950</strong></td>
<td>-</td>
<td><strong>206,464</strong></td>
<td><strong>16,639</strong></td>
</tr>
</tbody>
</table>

17. 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. Management is responsible for monitoring and supervising the substantial risks.

For risks related to accounting principles and financial reporting, an annual 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 risks related to accounting principles and financial reporting.

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

19. 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 summary 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.

20. AUDITORS
KPMG SA, Geneva, have been MMV’s statutory auditors since the fiscal year 2003. Following a competitive bid in 2017, KPMG were reappointed as the statutory auditors. The current lead auditor, Pierre-Henri PINGEON, has acted in this capacity since 2021. During fiscal year 2021, MMV incurred the following expenses:

- Statutory audits: USD 67,546 (2020: USD 81,588)
- Special audit reports to donors: USD 56,532 (2020: USD 62,445)

- Other services: USD 36,040 (2020: 25,759)

21. 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.
Behind the scenes 2021

MMV Board

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

Dr David Reddy† CEO, MMV, Switzerland

Dr Aileen Allsop Former VP and Head of the Infection Therapy area and VP Science Policy, both with AstraZeneca. Former Council member and Review Panel chair with the Royal Society of Biology, UK, and former Trustee of the Primary Science Teaching Trust. Chair of the UK government review of Science and Society. A member of ESAC for over 8 years and former Chair of Emerging Technology Reviews for MMV

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

Ms Jennifer Cain Birkmose Vice President, Global Head of Patient Access and Community Engagement, Swedish Orphan Biovitrum. INSEAD lecturer. Former Project Officer, European Observatory on Health Care Systems, WHO Regional Office for Europe

Mr Alan Court†‡ Vice-Chairman of MMV Board, Senior Adviser to the WHO Ambassador for Global Strategy, USA; Former Director of the UNICEF Programme Division in New York; Former Director of the UNICEF Supply Division in Copenhagen

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

Dr Winston Gutteridge Former Chief, Product R&D, Special Programme for Research and Training in Tropical Diseases (TDR), WHO, Switzerland; served as full MMV Board Member from 1999-2003 and again from March 2009; Chairperson, MMV Expert Scientific Advisory Committee (ESAC) from 2003-2009, UK

Ms Yuli Ismartono Co-founder and managing editor of the weekly online AsiaViews portal. Formerly with the weekly current affairs TEMPO magazine. Board member of Nature Resources Governance Institute (NRGI), the Coral Triangle Center (CTC), the Prestasi Junior Indonesia (PJI) foundation and the Alternative Association of Southeast Asian Nations (ALTSEAN), Indonesia

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

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

Ms Elizabeth Linder Founder & CEO, Chief Diplomatic Officer, Brooch Associates; Co-Chair, St. James Roundtable, Chatham House; Chair, Kinross House Meetings; Member, Ditchley Park Programme Committee; former Facebook Spokesperson and Politics & Government Specialist (California and EMEA region); former Google & YouTube Global Communications & Public Policy (California), Princeton University, USA/UK

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

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

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

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

Ambassador Dr Konji Sebat† (in memoriam) CEO, Innovative Pharmaceutical Association of South Africa (IPASA), Johannesburg, South Africa

Dr Elisabeth Svanberg Former Vice President of Established Products, Johnson & Johnson, USA; former Vice President of Medical Affairs Intercontinental Region, Bristol-Myers Squibb, USA; Board Member of Galapagos, Belgium; Board Member of Swedish Orphan Biovitrum (SOBI), Sweden. Now based in Geneva, Switzerland

* New Board Chair in December 2021
† Member of the Audit & Finance Committee
‡ Chair of the Audit & Finance Committee
** Chair of the Audit & Finance Committee
Expert Scientific Advisory Committee (ESAC)

Dr John Pottage
Co-Chairman MMV ESAC (Development); Chief Scientific and Medical Officer, VIV Health, UK

Dr Michael Witty
Co-Chairman MMV ESAC (Drug Discovery); Drug Discovery Consultant, UK

Dr Tesfaye Bitu
Distinguished Professor, National Institute of Pharmaceutical Sciences, Addis Ababa University, Ethiopia

Dr Nick Carmack
R&D Consultant, Medicines Development Campus for Diseases of the Developing World, GSK, Tres Cantos, Spain

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

Dr Robert Clay
Consultant/Managing Director, Highbury Regulatory Science Limited; and Board Member (President 2017) at TOFRA, UK

Ms Maeva Magner
Supply Chain Expert, USA/Ireland

Dr Viviana Mangiaterra
Associate Professor, SDA Bocconi School of Management, Italy

Dr Wilfred Mbacham
Fellow CAS/AAAS, Chair of Dept. of Physiology and Biochemistry, University of Yaoundé, Cameroon

Ms Delese Mimi Darko
Chief Executive Officer, Safety Monitoring & Clinical Trials Division, Food and Drugs Authority, Ghana

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

Dr Nick Fairhurst
Pharmacovigilance Medical Director, Chief Medical Office, Oncology R&D, AstraZeneca, USA

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

Dr Anne Cooper
Programme Director, Sosei Heptares, UK

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

Ms Delise Mimi Darko
Chief Executive Officer, Safety Monitoring & Clinical Trials Division, Food and Drugs Authority, Ghana

Dr Laurent Hennique
Former Research Director, Galderma R&D, La Tour de Peiz, France

Dr Robert Jacobs
Drug Discovery Consultant, Anacor Pharmaceuticals, USA

Dr Marcus Lacerda
Public Health Specialist, Fiocruz, Brazil

Dr Lynn Marks
Former Senior Vice President GSK R&D, USA

Dr George Mooney
Drug Discovery Consultant, USA

Dr Jetsumon Prachmusri
Head of Mahidol Vivax Research Unit (MVRU), Faculty of Tropical Medicine, Mahidol University, Thailand

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

Prof. Phil Rosenthal
Professor, Department of Medicine, University of California, San Francisco, USA

Access & Product Management Advisory Committee (APMAC)

Dr Martin De Smet (in memoriam)
Coordinator, the Malaria Working Group of Médecins Sans Frontières, Switzerland

Elizabeth Juma
Medical Officer, WHO (APMAC Observer), Ghana

Dr Corine Karema
Interim CEO, RBM Partnership to End Malaria, Switzerland

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

Dr David Reddy
CEO, MMV, Switzerland

Ms Sylvie Fonteilles-Drabek
Chair of MMV North America Board; General Counsel and Executive Vice President, Legal, MMV, Switzerland

Mr Andrea Buscaglia
Chief Financial Officer, MMV, Switzerland

Mr Alan Court
Senior Adviser to the WHO, Ambassador for Global Strategy, USA

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

Dr David Reddy
CEO, MMV, Switzerland

Dr Dennis Shanks
Director Australian Defence Force Malaria & Infectious Disease Institute, Australia

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Senior Research Fellow, Manože Health Research Centre, Mozambique

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Sieg Pharma Consulting, USA

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Drug Discovery Consultant, USA

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Independent Pharmaceutical Preclinical Safety Consultant at Preclinical Safety Consulting Ltd, UK

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Professor, Department of Medicine, University of California, San Francisco, USA

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Pharmaceutical Preclinical Safety Consultant, UK

Prof. Pieter Joubert
Clinical Pharmacology Consultant, UK

Dr John Pears
Director, Woodhouse Green, UK

Dr Lucette Dösssegger
Translational Drug Safety Consultant, Switzerland

Global Safety Board (GSB)

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

Dr Trevor Gibbs
Co-Chairman MMV Global Safety Board; Independent Consultant, UK

Prof. Tim Hammond
Pharmaceutical Preclinical Safety Consultant, UK

Prof. Pieter Joubert
Clinical Pharmacology Consultant, UK

Dr John Pears
Director, Woodhouse Green, UK

Dr Lucette Dösssegger
Translational Drug Safety Consultant, Switzerland

Dr Dennis Schmatz
Former Vice President and Head of Tsukuba Research Institute, Merck-Banyu Research Laboratories, Japan (now based in USA) Ambassador
MMV Team 2021

Executive Leadership Team & Support

Andrea Buscaglia, CFO, FA
Stephan Duparc, CMO, R&D
Sylvie Fonteilles-Drabek, EVP, Legal
George Jagoe, EVP, APM
Franziska Karyabwite, EVP, HR
Andrea Lucard, EVP, CA
Anya Ramalho, EVP, BD
David Reddy, CEO
Timothy Wells, CSO, R&D
Rana Rossignol, PA to the CSO
Helen Weir, PA to the CEO
Stefani Janvier-Ghouila, Executive Assistant

Access & Product Management (APM)

Emilie Alirol
Adam Aspinall
Céline Audibert
Pierre Hugo
Elodie Jambert
Melanie Larson
Maud Majeres Lugand
Hans Rietveld
Angela Sturgess
André-Marie Tchouatieu

Corporate Affairs (CA)

Jaya Banerji
Olaug Bergseth
Sylvie Dentand
Annah Espejo
Silvia Ferazzi
Peggy Letilly
Adrienne MacDonald
Charlie Masding
Neil McCarthy
Akolade Omishope
Abena Poku-Awuku
Elizabeth Poll
Valentina Rapillard
Murchana Roychoudhury
Danielle Sessa
Lindsay Seth
Klaudija Siciliano
Ivana Sirovic Aplon

Business Development (BD)

Nada Ariaepour
Sangeeta Bhagat
Nikolaos Chalkias
Joan Herbert
Sylwia Jarzebowska
Sandra Johnson
Beata Kusmider
Joe O’Sullivan

Finance & Administration (FA)

Soazig Bertrand
Grégoire Bonnaud
John Clare
Marie-Ange Coustets
Gelavizh Daghf
Mélanie Dupuy
Perine Georges
Elizabeth Kemen
Brigitte Laude
Jean-Christophe Magnin

Human Resources (HR)

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Wendy Redford
Veronique Reusse
Anna Valasidi

Legal

Maud Dusan
Lorelei Garagancea
Lorena Gesto Gende
Eric Justafre
Aleksandra Kalentic
Simona Mag Valigova
Allison Neapole
Dragana Obrenovic
Hella Pisani
Alicja Poczatkenko
Tareq Sunderji

Research & Development (R&D)

Discovery
Delphine Baud
Dominique Besson
Stephen Brand
Jeremy Burrows
Brice Campo
Elodie Chenu
Angelique Doy
Maëlle Duffey
James Duffy
Benoit Lalou
Didier Leroy
Zaira Rizopoulos
Mélanie Roullier
Anna Sulakova
Paul Willis

Translational
Nada Aba Geiser
Catalina Barcelo
Benoit Bestgen
Mohammed Cherkaoui
Helen Demarest
Claudia Demarta-Gatsi
Ilaria Di Resta
Cristina Donini
Emilie Escoffier
Nathalie Gobert
Jacques Hervé
Sam Jones
Nicolas Martinier
Jörg Möhrle
Andrew Slade
Belen Tornesi

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Farouk Chughlay
Anne-Claire Marrast

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Isabelle Borghini-Fuhrer
Myriam El Gaaloul
Amina Haouala
Wiweka Kaszubskas
Andrea Kuebler
Fiona Macintyre
Vitalia Mitrovic
Alice Neequaye
Hau Ramachandrani
Anouchka Smits Bayala
Anna Thomas
Florian Wartha
MMV is grateful for the support in 2021 from our institutional donors.

MMV is also grateful for the support received from private individuals.