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REPORT
2014



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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 and registered in Switzerland.

MMV's mission

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

MMV's vision

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

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Poster:

Key achievements over the last 15 years

MMV-supported projects – 4th quarter 2014



Mr Ray Chambers
Chairman of the Board

Dr David Reddy
MMV's CEO

1

Breaking the cycle

Message from the Chairman and CEO

“ We should all be concerned about the future because we have to spend the rest of our lives there.”

Charles F Kettering
American engineer

Malaria and poverty are inextricably linked. The disease hinders economic development in many regions, trapping others in a seemingly endless cycle of poverty. We witness the link whenever we travel in endemic countries. In a mountain village in Cambodia, a soya bean farmer explained he had suffered from malaria five times in 2014 and was sick yet again (page 19). As the main breadwinner, when he has malaria, he can't work and struggles to put food on the table for his wife and children. The story was similar on the other side of the world, on the banks of the Amazon in Peru. A mother explained she could not earn her daily living selling chicken broth when her young children have malaria; she has to stay at home and care for them.

Malaria affects not just individuals and families, but communities and economies. People living an already precarious existence are struggling against this debilitating disease, not just in Cambodia and Peru, but in 97 countries – half of all countries in the world.

Each of us committed to ending malaria is fuelled by a vision of a better world, one where no child dies before his or her fifth birthday because of a mosquito

bite; where no parent loses the ability to provide for their children because they are too ill to work; and where development is not hindered by disease.

MMV is committed to playing its part in the fight against malaria by discovering, developing and delivering new and better medicines to help break the cycle of malaria and poverty. The good news is that we are making extraordinary progress.

Working with our partners we have taken giant strides towards a single-exposure cure for both uncomplicated and relapsing malaria. OZ439 has progressed to a phase IIb trial with Sanofi (page 14), and tafenoquine, for the liver-stage of relapsing malaria, is currently in phase III trials with GSK (pages 18–19) and progressing ever closer to regulatory filing. In total, we have nine new molecules in clinical development addressing these and other unmet needs. Each holds the promise of a new medicine that could improve the quality of life and the future of those most affected by malaria.

Today, we are reaping the benefits of extensive screening efforts, with many novel antimalarial compounds progressing through the portfolio.

This allows us to choose only those that meet stringent target profiles (pages 8–9). In addition, together with our partners, we have established innovative enabling technologies such as the Controlled Human Malaria Infection Model (page 13) to provide us with new insights and answers to make that selection quick and cost-effective.

With increased understanding of the malaria parasite's biology, we have been able to identify new points at which to break the parasite's lifecycle. In addition to conventional blood-stage assays¹ or tests, new assays recapitulating the biology at these points leading to infection and transmission have been developed and are being used to screen increasing numbers of compounds for new attributes. In this way, we are advancing the science of malaria elimination and eradication. Piecing together emerging data from these assays could help us find a molecule active against all lifecycle stages.

One such molecule may have already been identified: DDD498, discovered through a collaboration with the University of Dundee's Drug Discovery Unit, has been awarded MMV's Project of the Year 2014 (pages 24–25).

Meanwhile, the five medicines MMV and partners have developed and brought forward to date are already being used to treat people across the globe from Cambodia to Nigeria to Peru, and saving lives. More than 255 million treatments have been delivered since 2009 – the vast majority for children.

The availability of these life-saving treatments, alongside vector control measures, has undoubtedly assisted the global community to achieve Millennium Development Goal 6.C,² to halt and begin to reverse the incidence of malaria by 2015. Owing to the increased and effective delivery and use of malaria interventions since 2000, the incidence of the disease has fallen by 30% globally, with a 47% decline in global mortality. Step by step, we are getting closer to breaking the cycle of malaria and poverty.

This achievement deserves acclaim. Yet, we must remember that the past is a springboard, not a hammock. We have no time to rest on our laurels while people continue to die of malaria and global development continues to be hindered. Moreover, as we progress towards elimination and eradication, the demands placed on medicines will change; for example, immunity will start to decline and the need for new types of chemopreventive medicines will grow.

As the MDGs transition to the Sustainable Development Goals (SDGs)³ in 2016, MMV's priorities too are evolving. We will focus less on developing artemisinin combination therapies and more on next-generation antimalarials. These future medicines will break the cycle of relapsing malaria, overcome the challenges of compliance and drug resistance, and protect vulnerable populations. In doing so, they will support the realization of the proposed SDG 3 – to ensure the sustainability of healthy lives and wellbeing for all, at all ages.

And while the goals have yet to be finalized, we, the global health community must advocate for health to feature high on the agenda. Health is after all, the foundation of all sustainable development.

Our goal to break the cycle of malaria and poverty by developing and delivering new medicines is certainly ambitious and MMV is but a small organization of 55 individuals. Yet, thanks to our ever-growing network of partners and donors, who are as committed as MMV to the fight against malaria and as concerned about the future of global health, we are stronger, more effective and more resolute. Together we are determined to build a better, healthier future for our children; a future where malaria is a disease of the past. And moreover, we are determined to succeed. ●

¹ Assay: a procedure for measuring the biological activity of a substance, in this case the activity of a compound against the malaria parasite.

² The Millennium Development Goals (MDGs) are eight international goals established following the Millennium Summit of the United Nations (UN) in 2000. All 189 UN member states at the time (there are 193 currently), and at least 23 international organizations, committed to help achieve the MDGs by 2015: <http://www.un.org/millenniumgoals/>

³ The Sustainable Development Goals (SDGs) are a new, proposed, universal set of goals, targets and indicators that UN member states will be expected to use to frame their agendas and political policies over the next 15 years: <https://sustainabledevelopment.un.org/sdgsproposal>



Key achievements over the last 15 years



- Bill & Melinda Gates Foundation
- Swiss Government SDC
- Rockefeller Foundation
- ExxonMobil Foundation
- UK Department for International Development
- World Bank

- World Health Organization/ Roll Back Malaria (WHO/RBM)
- Netherlands Minister for Development Cooperation

- Wellcome Trust

- BHP Billiton
- United States Agency for International Development

- Irish Aid

1999

2000

2001

2002

2003

2004

2005

2006

FIRST PLEDGES BY MMV DONORS

2012

4th medicine: **Pyramax®** for uncomplicated malaria (partner Shin Poong) receives positive scientific opinion from EMA

Eurartesim® used in Cambodia to help **contain drug resistance**

Malaria Box launched to catalyse malaria and neglected disease drug research

3rd medicine: **Eurartesim®** for uncomplicated malaria (partner Sigma-Tau) receives EMA approval

2011

Controlled Human Malaria Infection Model comes on stream at QIMR Berghofer in Australia to accelerate drug development: drug candidates are tested in healthy individuals infected with malaria in carefully controlled conditions

1st molecules with potential for **chemoprotection** (**KAF156** with Novartis and **DSM265** with NIH and Takeda) enter clinical development

230+ copies of the **Malaria Box** delivered to research groups globally

2013

50+ team members working with a global network of **375+** partners

Global malaria mortality down by 47% from 2000

2014

1 donor dollar = USD 3.5 investment impact thanks to direct and in-kind support

5th medicine: **Guilin's SP+AQ** for 1–5 year olds receives WHO prequalification

1st antimalarial molecule discovered by an African-led team, **MMV048**, begins human trials

Tafenoquine to treat the liver-stage of relapsing malaria enters phase III

OZ439 and piperaquine, a potential single-exposure antimalarial combination enters phase IIb

9 new medicines in clinical development prioritizing eradication and the needs of vulnerable populations

250 million courses of Coartem® *Dispersible* delivered to treat children in 50 countries

36 million vials of Artesun® delivered, estimated to have saved an additional 200,000–240,000 lives compared to treatment with quinine

- Norwegian Agency for Development Corporation
- Global Health Innovative Technology Fund
- MerckSerono
- UNITAID
- Australian Government Department of Foreign Affairs and Trade

- Newcrest Mining Limited
- MJC Amelior Foundation

- Technology Innovation Agency (TIA), South Africa

- National Science and Technology Development Agency (NSTDA), Thailand

- Spanish Agency for International Development

- National Institutes of Health

2007

2008

2009

2010

2011

2012

2013

2014

MMV strategic overview: developing medicines for today and tomorrow

MMV's work focuses on how medicines can reduce the overall burden of malaria. That means looking at how we can save more lives today by treating more people with currently available medicines (pages 26–31). This includes ensuring that formulations and supportive data are available to facilitate optimal use of interventions in children and pregnant women – the most vulnerable populations. However, the goal to eradicate malaria needs improved next-generation medicines with new attributes.

Given the long-term nature of research and development (R&D) it is important to know at the very outset what success looks like – this is described by the Target Product Profiles (TPPs). The Malaria Eradication Research Agenda (malERA) initiative¹ drew on the knowledge of malaria experts from around the world to define two key TPPs for medicines needed to make eradication possible:

- TPP1 – Single Exposure Radical Cure and Prophylaxis (SERCaP), a medicine able to kill the parasite at all lifecycle stages, thus preventing relapse and stopping transmission, that is also effective against resistant strains of malaria and will help improve compliance.
- TPP2 – Single Exposure Chemoprevention (SEC), which has a different mechanism of action to treatment.

An added complication for a new antimalarial medicine is that it consists of several active ingredients. To develop individual novel candidate compounds that can be combined into one product in line with these TPPs, MMV has defined five Target Candidate Profiles (TCPs), which correspond to the different clinical attributes needed for eradication (see legend below).

To identify molecules to meet these TCPs, MMV and partners have developed a

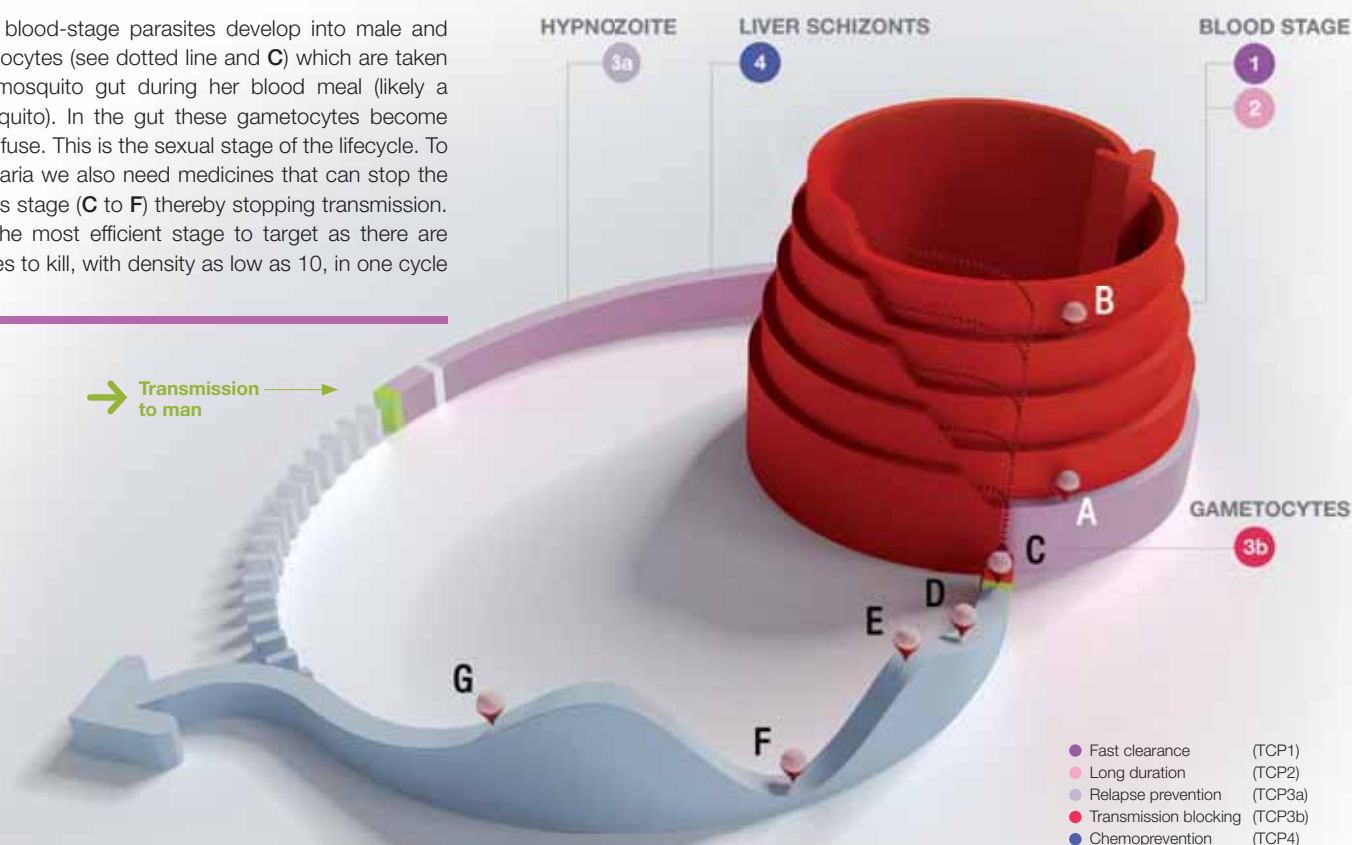
series of assays to screen for activity at each of the critical points in the parasite lifecycle. In the asexual blood-stage assay, more than 6 million molecules have been tested. This initiative has brought forward molecules with the potential to form a single-exposure cure and to tackle drug resistance in the medium-term, and assays to deliver a SERCaP in the long-term (pages 20–23).

During 2014, in an unprecedented step, with support from the Japanese Global Health Innovation Technology (GHIT) Fund, MMV and partners collaborated with Daiichi-Sankyo, Takeda and Eisai to screen 90,000 novel compounds against both the blood and liver stages of malaria. The combination of accessing novel chemical diversity and screening directly on liver stages has led to the identification of new chemical series. As a result, Daiichi-Sankyo is working on a new project funded by GHIT to identify promising lead compounds. ●

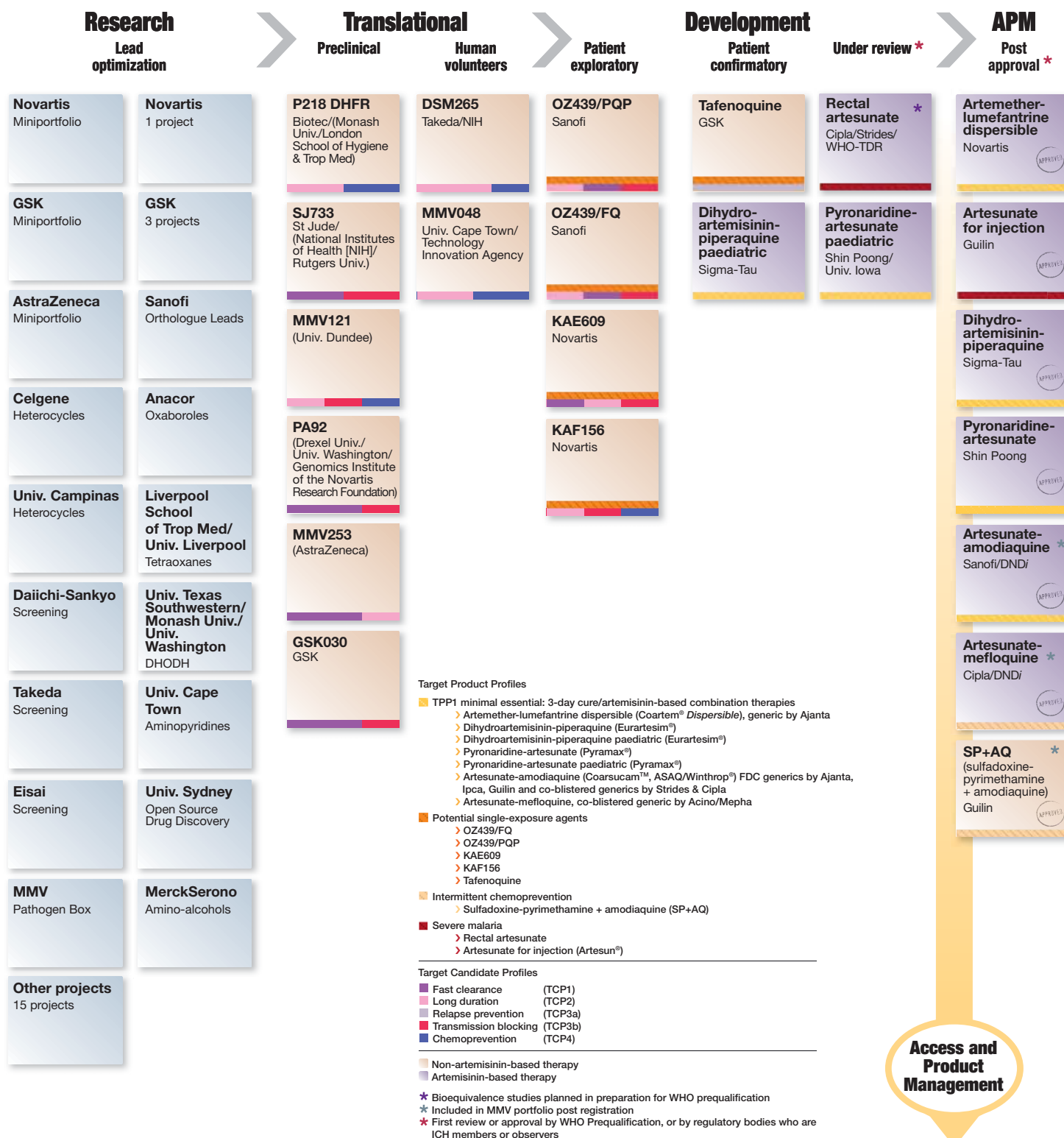
¹ malERA Consultative Group on Drugs. "A research agenda for malaria eradication: drugs". *PLoS Med.* 8(1):e1000402 (2011).

The malaria parasite is transmitted to humans (→) by a female *Anopheles* mosquito when she takes a blood meal to feed her young. The parasites are rapidly taken up into the cells of the liver where they become schizonts (A), multiply and go on to invade blood cells. Current medicines mostly kill malaria parasites at this blood stage. This is when the parasite is at its most abundant – up to 10^{12} parasites in one person (B) and the stage that leads to the clinical symptoms of malaria.

Some of the blood-stage parasites develop into male and female gametocytes (see dotted line and C) which are taken up into the mosquito gut during her blood meal (likely a different mosquito). In the gut these gametocytes become gametes and fuse. This is the sexual stage of the lifecycle. To eradicate malaria we also need medicines that can stop the parasite at this stage (C to F) thereby stopping transmission. This is also the most efficient stage to target as there are fewer parasites to kill, with density as low as 10, in one cycle of infection.



MMV-supported projects – 4th quarter 2014





2

Maintaining momentum and building on gains

Dr Pedro L Alonso

Director, Global Malaria Programme,
World Health Organization

Can we eradicate malaria from the world? I believe we can and what's more, I believe it's the only morally acceptable goal. Combating malaria is not only key to saving many hundreds of thousands of lives each year, it's also key to improving equity, social justice and the economy in some of the world's poorest countries.

It is these beliefs that compelled me to take up the position of Director of the Global Malaria Programme (GMP) in 2014. To achieve eradication we must put the wheels in motion now. We must identify and fill the gaps in knowledge and tools and coordinate global efforts. That's where the Global Malaria Programme comes in.

Over 4 million malaria deaths have been averted since 2000 and the Millennium Development Goal 6, to halt and reverse the incidence of malaria globally by 2015, has been met. This is thanks to increased political commitment and financing, enabling the scale-up of core malaria control interventions and the development of new and better tools.

Yet, we still have a long way to go – around 3.2 billion people continue to live at risk and 50 lives are lost to malaria every hour. What's more, there are many challenges to overcome along the way. Increasing parasite resistance to drugs and mosquito resistance to insecticides threaten to render current tools ineffective and may increase the death toll from malaria. Strengthening health systems, including surveillance systems and the health workforce, will require massive new financial resources and long-term political commitment by some of the poorest countries in the world.

Time for a new strategy

The world has reached a critical juncture in the fight against malaria. A powerful and coordinated global response and continued investment in research and development is needed now.

To accelerate progress, GMP developed a new global technical strategy for malaria (2016–2030), which was adopted by the World Health Assembly in May 2015. The strategy sets a new target of reducing global malaria incidence and mortality rates by at least 90% between 2016 and 2030. We can achieve this through three pillars of work:

Pillar 1: Ensuring universal access to malaria prevention, diagnosis and treatment

Pillar 2: Accelerating efforts towards elimination and attainment of malaria-free status

Pillar 3: Transforming malaria surveillance into a core function

Where do medicines fit in?

The role of current medicines and the development of new ones are critical to each pillar of work.

We must substantially expand access by malaria patients to diagnosis and quality-assured WHO-recommended treatment. The work of MMV and partners has been critical in this area. It has enhanced the global antimalarial tool kit with five additional quality-assured medicines and these medicines are already saving lives today.

“Around 3.2 billion people continue to live at risk and 50 lives are lost to malaria every hour.”

To maintain the momentum, we must keep our eye on emerging threats, such as drug resistance, and ensure the development of new medicines for the future. We need to protect the efficacy of artemisinin combination therapies and develop new combinations. History has taught us that the long-term usefulness of any medicine or combination of medicines is threatened by the emergence and spread of drug resistance. This is where a robust pipeline of new medicines for the future is vital. Thanks to MMV's persistence and diligence, the global antimalarial R&D pipeline is in a better position today than ever before.

To be able to build on the gains and develop tools needed for malaria elimination and eradication, the pipeline needs to be continually

populated with promising antimalarial compounds that have the potential to be developed into new kinds of medicines. To reduce the overall burden of malaria, we need medicines that can block transmission of the disease and be used in mass drug administration campaigns. To protect vulnerable populations, such as pregnant women and children, we need medicines that are extremely safe and active against the liver stages of malaria. To put an end to the relentless malaria relapses of *P. vivax* we will need new medicines to target its dormant reservoirs.

These are the medicines that together with accurate diagnostics, novel insecticides and future vaccines can make the goal of malaria eradication a reality.

Whether we can eradicate malaria is indeed a big question. However, for me the real question is not if, but how. The new GMP strategy aims to answer this question in practical terms: we need to optimize the use of current tools to maintain the momentum, and develop and roll out new tools to build on the gains. But the bottom line is that all of this can only be achieved, and malaria – can and will – only be eradicated, in partnership. International donors, the private sector, academia, product development partnerships and civil society groups, need to work together, keeping malaria-endemic countries at the heart of the effort. ●

“ Malaria can – and will – only be eradicated, in partnership ”





3

Developing next-generation medicines

Overcoming resistance

ISSUE

In some regions, we are seeing increasing reports of resistance to both components (multidrug resistance) of current first-line artemisinin-based combination therapies (ACTs), resulting in an overall reduction in the efficacy of treatment and in some cases, treatment failure.¹

In addition, current treatments must be taken over 3 days, and several studies suggest that, as a result, adherence is often sub-optimal.² This can lead to incomplete cure and encourage the emergence of drug resistance.

ACTION BY MMV AND PARTNERS

Identify and develop new molecules with novel mechanisms of action to overcome drug resistance, prioritizing candidates that are both fast and long-acting for combination into a single-exposure cure in the medium term and a Single Exposure Radical Cure and Prophylaxis (SERCaP) in the longer term.

One of the biggest challenges in the treatment of malaria is parasite resistance to drugs and insecticides. Resistance to artemisinin, the backbone of today's gold-standard ACTs, has now been detected in Cambodia, Laos, Thailand, Vietnam, Myanmar and recently along India's borders.³ This geographical spread, combined with the emergence of multidrug-resistant strains showing decreased susceptibility to both the artemisinin derivatives in tandem with the partner drugs, such as mefloquine and more recently piperazine, is of grave concern.⁴ If unchecked, we may witness the emergence of a drug-resistant malaria epidemic, with the potential to undermine years of steady progress in the fight against malaria.

Another concern is that patients often do not complete their course of treatment. The currently recommended medicine is administered once or twice daily for 3 days. However, since symptoms usually improve rapidly, the danger, for example, is that a mother may save the remainder of the treatment for the next time her child is infected. This is understandable, given that for some patients, even low-cost drugs can be challenging to access. In addition, in some parts of Africa a child may succumb to malaria as often as 26 times in 2 years⁵ and often not receive a complete cure – a situation that can encourage the emergence of drug resistance.

To overcome these two key concerns MMV is seeking and developing new molecules with new mechanisms of action, which would be fully active against all known resistant strains. Our new compounds are all fast-acting, some as fast, and even faster, than the artemisinins. In addition, they have all been selected for their long duration of action, and so could be part of a SERCaP. The availability of a SERCaP for malaria would allow directly observed treatment and would greatly enhance the operational feasibility of malaria-elimination programmes.

- 1 Phyto AP *et al.* "Emergence of artemisinin-resistant malaria on the western border of Thailand: a longitudinal study." *Lancet* 379(9830): 1960-6 (2012).
- 2 Bruxvoort K *et al.* "How patients take malaria treatment: a systematic review of the literature on adherence to antimalarial drugs." *PLoS One*. 9(1):e84555 (2014).
- 3 Tun KM *et al.* "Spread of artemisinin-resistant *Plasmodium falciparum* in Myanmar: a cross-sectional survey of the K13 molecular marker." *Lancet Infect Dis*. 15(4):415-21 (2015).
- 4 Bustos MD *et al.* "Monitoring antimalarial drug efficacy in the Greater Mekong Subregion: an overview of *in vivo* results from 2008 to 2010." *Southeast Asian J Trop Med Public Health*. 44 Suppl 1:201-30; discussion 306-7 (2013).
- 5 Yeka A *et al.* "Efficacy and safety of fixed-dose artesunate-amodiaquine vs. artemether-lumefantrine for repeated treatment of uncomplicated malaria in Ugandan children." *PLoS One*. 1;9(12):e113311 (2014).



Dr Didier Ménard
Head, Malaria
Molecular
Epidemiology
Unit, Institut
Pasteur in
Cambodia.

Dr Didier Ménard and his team have developed an *in vitro* assay to enable in-development antimalarials to be tested against the most resistant strains of parasite we know of today.¹ Building on this work the team was also able to identify a molecular marker to identify artemisinin-resistant parasites,² which is now being used to map artemisinin resistance globally. He explains why drug resistance is such a problem, how the assay works and what it has told us so far.

Q Why is drug resistance such a problem in the treatment of malaria?

Drug resistance is a major threat to the control and elimination of malaria. The emergence and spread of chloroquine-resistant parasites illustrates the issue. The first resistant parasite emerged along the Thai-Cambodia border in the 1960s and it spread to Africa in the 80s. We saw a huge increase in mortality. Drugs are the main tools we have to fight against malaria. If you use ineffective treatment, people will die.

Q How did you develop the *in vitro* resistance assay?

Previously, we used a classic *in vitro* test, where the parasite was exposed to different concentrations of the drug (0–60 nM) during its 48 h lifecycle. There was discordance between the findings of this test and those of the clinical studies. At Institut Pasteur in Cambodia, we developed a new assay emulating the conditions the parasite actually experiences in human beings. The half-life of artesunate in humans is short, and so we exposed the parasites to the concentration we'd see in patients after a single dose (700 nM) for just a short time of 6 hours.

We developed the assay, which we call the ring-stage survival assay, RSA^{0-3h} and were really excited to see that OZ439 is active. Further work has shown just how strongly associated the results are to clinical data. We see a high survival rate of parasites from patients with a slow parasite clearance rate and vice versa. We are now able to characterize and distinguish resistant and sensitive parasites in the lab.

Q Which molecules from MMV's portfolio have you been able to test and what have you found?

So far, we have tested OZ439, ferroquine and a couple of preclinical molecules. We have made an extensive evaluation of OZ439. To me it's a wonderful molecule. It's very efficient against artemisinin-resistant parasites and works quickly and efficiently. It gives us hope. It could be a very interesting alternative to artemisinin.

We have also evaluated new partner drugs, such as ferroquine. This is a good potential partner. It is totally effective against malaria; we will need to do more tests to determine its efficacy against resistant strains.

Q How was the molecular marker for artemisinin resistance identified?

Colleagues at Institut Pasteur in Paris sequenced a parasite strain that had been cultured under pressure and become resistant to artemisinin. We then compared the genomes of this strain with its parent (non-exposed to artemisinins) and found mutations in eight genes that could be involved in drug resistance.

In Cambodia, we then checked to see if these genes were also mutated in isolates from patients. We found that only mutations in one gene (Kelch gene on the chromosome 13 [named K13], which was clearly associated with artemisinin resistance) were expressed in the new *in vitro* assay (RSA^{0-3h}). In Pailin, on the Thai-Cambodia border, we have seen an increase in the mutant parasite since 2002, which coincides with the increase in artemisinin resistance. While in provinces without delayed parasite clearance time, we see parasites with no mutation in the K13 gene.

It took a combination of genomic, epidemiological, clinical and biological expertise to confirm that the mutation in the K13 gene was strongly associated with artemisinin resistance.

Q What's it been like working with MMV?

It's very easy to work with MMV. The people are smart and we share the same goal: to get results. The lab is tough; you can't just push a button and get results. They understand that. If we have a problem we work together to find a solution.

Our job is to characterize drug resistance, raise the issue, and develop tools to detect it. With MMV, we also have the possibility to help develop a solution: next-generation antimalarials that are effective against the resistant parasites. ●

Controlled Human Malaria Infection Model

This model was originally developed with Prof. James McCarthy from QIMR Berghofer Medical Research Institute, Queensland, Australia, to test candidate medicines for blood-stage activity in volunteers inoculated with a small dose of malaria in a tightly controlled environment. It provides a granularity of data previously inaccessible, allowing us to quickly understand whether a compound will work in humans and provide guidance on dose selection for subsequent studies.

The model has now been adapted to look at combinations of new molecules. A study looking at OZ439 with DSM265 is planned for 2015. The study will inform us on how the combination acts on parasites in humans and whether the antiparasitic effects are additive, synergistic or antagonistic. This type of study will inform the selection of partner drugs and their doses for further development. The planned study will have a direct impact on how the combination of OZ439 and DSM265 will progress. We are also looking at whether the model can be used to study the effects of drugs on gametocyte formation, a key step to understanding which molecules have transmission-blocking activity (page 22).

“(OZ439) To me it's a wonderful molecule. It's very efficient against artemisinin-resistant parasites and works quickly and efficiently.”

¹ Witkowski B *et al.* "Novel phenotypic assays for the detection of artemisinin-resistant *Plasmodium falciparum* malaria in Cambodia: *in-vitro* and *ex-vivo* drug-response studies." *Lancet Infect Dis.* 13(12):1043-9 (2013).
² Aries F *et al.* "A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria." *Nature* 2;505(7481): 50-5 (2014).

OZ439 (artefenome)l

Patient exploratory (phase IIb)

Target indication:

Part of combination treatment for uncomplicated malaria

Key features:

- Fast reduction of parasites, similar to artemisinin
- Active against all drug-resistant strains of malaria, including artemisinin-resistant
- Active concentrations achieved for over a week from a single exposure, therefore potential for a single-exposure treatment in combination¹
- Potential to block transmission, based on preclinical data²

Project Leader: Dr Marc Adamy, MMV

Sanofi Project Head: Rita Merino

OZ439/4-aminoquinoline development partner: Sanofi

Discovery partners: University of Nebraska Medical Center, USA; Monash University, Australia; Swiss Tropical and Public Health Institute, Switzerland

1 Moehrle JJ *et al.* "First-in-man safety and pharmacokinetics of synthetic ozonide OZ439 demonstrates an improved exposure profile relative to other peroxide antimalarials." *Br J Clin Pharmacol.* 75(2):524-37 (2013).

2 Delves M *et al.* "The activities of current antimalarial drugs on the life cycle stages of *Plasmodium*: a comparative study with human and rodent parasites." *PLoS Med.* 9(2):e1001169 (2012).

In 2014, our front-runner compounds with single-exposure potential continued to progress through the pipeline, taking us closer to a next-generation antimalarial treatment.

OZ439 or artefenome)l, a molecule MMV has progressed right from discovery, is now in phase IIb combination studies with piperaquine (PQP) as a single-exposure cure in partnership with Sanofi. As children are the target population for the medicine, the OZ439-piperaquine phase IIb trial adopts a staggered approach obtaining safety data first in adults before progressing to older, then younger children, expediting the development programme. The trial is progressing well; in March 2015, a third review of the data by an Independent Safety Monitoring Board allowed recruitment to begin of children in the lowest age group (≥ 6 months to ≤ 2 years).

OZ439 will also be tested in combination with another 4-aminoquinoline, ferroquine, a novel antimalarial being developed by Sanofi. This second phase IIb trial is due to start in 2015. Following the results of the two studies, a decision will be taken regarding which combination to take forward into phase III studies.

Encouraging, *in vitro* data from the first artemisinin-resistance assay indicates that the compound is active against resistant strains at clinically relevant concentrations. These findings, however, will still need to be confirmed in patients.

Q What are the biggest challenges the team faces in the development of this next-generation antimalarial?

Primarily, it's the time pressure. We are working to get a new antimalarial to patients before drug resistance overwhelms us.

Then in terms of the development itself, the biggest challenges relate to the product characteristics. For example, OZ439 has low water solubility and PQP has a bitter taste, yet, we need to develop a formulation that can be easily absorbed and is palatable. Also, a new OZ439/4-aminoquinoline medicine would be a combination drug with at least one new chemical entity (i.e. OZ439+piperaquine, a well-known antimalarial) or two new chemical entities (OZ439+ferroquine). All the ACTs we use today were developed using two established chemical entities.

Q How will you overcome these challenges?

MMV and Sanofi are working together to solve these formulation issues by leveraging Sanofi's chemistry, manufacturing and control (CMC) expertise and MMV's experience and knowledge. We had a great meeting in September with specialists and people from five other pharmaceutical companies to seek out the best solutions.

Q What is the value-add of working with MMV as a partner?

MMV provides essential insights and expertise in the field of malaria drug research and development. In addition, it is focused on ensuring its products have the greatest possible public health impact – to save lives. MMV also has an extensive network of research partners and national and international policy-makers. I am delighted to say we are already seeing the benefit of these links, insights and expertise in the field of malaria. ●



Rita Merino
OZ439/4-aminoquinoline Project Leader at Sanofi, explains the challenges in the development of this next-generation medicine and what it's like to work with MMV.

“(MMV is) focused on ensuring its products have the greatest possible public health impact – to save lives.”



Dr Queen Dube
Paediatrician,
Queen Elizabeth
Central Hospital,
Blantyre,
Malawi, explains
the malaria
burden in
Malawi and the
ideal medicine
to treat it.

Q How often do you see children with malaria coming into your clinic?

It varies with the season, but it's a daily occurrence. During the rainy season, we're talking about 50 plus kids, mostly under the age of 2, coming through our doors on a daily basis. Once the rains have stopped we could be talking about 30 or thereabouts.

Q What's the effect of malaria on families and communities?

The effect is huge. When it's a little one, the mother will be here all the time, maybe leaving other little ones at home. If she was working, she'd have to take some time off. She may end up with a disabled kid. If you have a disabled child in a setting like ours it's tough. We don't have support for disabled children. It's difficult for the family. For simple cases, they get their drug and the family goes back to normal. It's the severe cases where, at the end of the day, it's not just this one child but the entire family that suffers.

Q What would be the ideal medicine to treat these children with malaria?

You want something that will clear parasites quickly, something that is palatable. With malaria, we're talking about children and some of them cannot swallow a tablet. You want something that doesn't have to be given over 3 days or longer. A single-exposure would be ideal. You give the medicine and you can forget about it. Once you go beyond a day, 2 or 3 days you can't be sure they will finish the course. In short, you want something that is effective at killing the parasite quickly with very few side-effects, preferably a palatable, single-exposure cure. ●

“...you want something that is effective at killing the parasite quickly...”



Trifhonia's story, Malawi

Trifhonia Idrissah lives near Blantyre, Malawi, with her husband and four children. Her children suffer from malaria up to six times a year. To make a living, Trifhonia sells duvets, shoes and clothes. When one of her children is sick with malaria she can't work. She spends time and money caring for her sick child and worries about not being able to provide for the others.



KAE609

Patient exploratory (phase II)

Target indication:

Part of a combination treatment for acute uncomplicated malaria

Key features:

- Novel acting with potential to treat artemisinin-resistant strains of malaria
- Potential for a single-exposure treatment in combination with a partner drug¹
- Rapid parasite and fever clearance in uncomplicated malaria patients²
- Potential to kill gametocytes and block transmission³

Project Leader: Dr Giancarlo Francese, Novartis Pharma AG

MMV Project Director: Dr Isabelle Borghini-Fuhrer

Development partner: Novartis Pharma AG

Discovery partners: Novartis Institute for Tropical Diseases, Singapore; The Wellcome Trust, UK; Swiss Tropical and Public Health Institute, Switzerland; Biomedical Primate Research Institute, the Netherlands; Genomics Institute of the Novartis Research Foundation, USA

KAF156

Patient exploratory (phase II)

Target indication:

Part of a combination treatment for acute uncomplicated malaria

Key features:

- *In vitro* activity against liver schizonts and potential for chemoprophylaxis⁴
- Potential for a single-exposure cure and therefore improved patient adherence to treatment

Project Leader: Dr Roger Waltzmann, Novartis Pharma AG

MMV Project Director: Dr Jörg Möhrle

Development partner: Novartis Pharma AG

Discovery partners: Genomics Institute of the Novartis Research Foundation, USA; the Wellcome Trust, UK; Swiss Tropical and Public Health Institute, Switzerland; Biomedical Primate Research Institute, the Netherlands

DSM265

Patient exploratory (phase II)

Target indication:

Part of a combination treatment for acute uncomplicated malaria

Key features:

- Novel mechanism of action, inhibiting the enzyme dihydroorotate dehydrogenase (DHODH). Fully active against all field isolates including artemisinin-resistant strains of malaria
- Active plasma concentrations can be maintained for more than one week following a single dose, so could be part of a single-exposure combination
- *In vitro* data against liver schizonts showing potential for prophylaxis

Project Leader: Dr Thomas Rueckle, MMV

Partners: University of Texas Southwestern, USA; University of Washington, USA; Monash University, Australia; AbbVie, USA; Takeda Pharmaceutical Company Ltd, Japan

MMV048

Human volunteers (phase I)

Target indication:

Part of a combination treatment for acute uncomplicated malaria

Key features:

- Highly potent against *P. falciparum* blood-stage malaria, activity seen with doses of 20 mg
- Good prophylactic activity against *P. cynomolgi* (surrogate for *P. vivax*) *in vivo* after a single exposure

Project Leader: Dr Cristina Donini, MMV

Partners: University of Cape Town, South Africa; Technology Innovation Agency (TIA), South Africa

- 1 Rottmann M et al. "Spiroindolones, a potent compound class for the treatment of malaria." *Science*. 329(5996):1175-80 (2010).
- 2 White NJ et al. "Spiroindolone KAE609 for falciparum and vivax malaria." *N Engl J Med*. 371(5):403-10 (2014).
- 3 van Pelt-Koops JC et al. "The spiroindolone drug candidate NITD609 potentially inhibits gametocytogenesis and blocks *Plasmodium falciparum* transmission to anophelous mosquito vector." *Antimicrob Agents Chemother*. 56(7):3544-8 (2012).
- 4 Meister S et al. "Imaging of *Plasmodium* liver stages to drive next-generation antimalarial drug discovery." *Science*. 334(6061):1372-7 (2011).
- 5 With support from the German Center for Infection Research (DZIF).
- 6 With support from the United States Department of Defense.
- 7 With support from the Global Health Innovation Technology (GHIT) Fund.

DSM265

is a triazolopyrimidine-based highly selective inhibitor of *Plasmodium*'s dihydroorotate dehydrogenase (DHODH), a key enzyme for the parasite's survival. In January 2015, the compound entered a phase IIa clinical trial in Iquitos, Peru. Here, its activity in both *P. falciparum* and *P. vivax* malaria patients is being put to the test.

Preliminary results from the trial are very encouraging.

In parallel, the potential of DSM265 as a novel chemopreventive agent is being assessed in two experimentally-induced infection studies, in collaboration with Prof. Peter Kremsner in Germany⁵ and Dr Jim Kublin in the USA.⁶ The compound is being progressed in collaboration with Takeda Pharmaceutical Company, Japan.⁷



Dr Martin Casapia
Asociación Civil Selva Amazónica (ACSA), Iquitos, Peru;
Co-Investigator for the DSM265 phase IIa trial.

Q What is the burden of malaria and its impact in Peru?

In Peru, there are around 50,000 malaria cases a year, mostly in the jungle, where it is endemic. We have both *P. vivax* and *P. falciparum* malaria, but much more *P. vivax* – around 70–80%.

It has a big impact, as morbidity is very high. Patients are not able to work or perform their regular activities when they are suffering. They lose many days of work and many of them suffer repeatedly. People usually have infection several times per year; in many cases five times a year or even as much as 10 or 20 times.

Q What is the current treatment in Peru and how do patients react to the regimen?

Treatment for *P. vivax* is chloroquine+primaquine and for *P. falciparum* its artesunate+mefloquine.

Adherence is definitely a problem, more so for *P. vivax* than *P. falciparum*. Primaquine for *P. vivax* should be taken for 7 days, but patients often take the treatment for 3 days and no more. The reason is that patients get much better quickly and then don't want to take more pills. They might feel it's dangerous to take pills for lots of days. Nevertheless, we do work hard to encourage compliance.

Q What would be the ideal antimalarial medicine for Peru?

An ideal medicine would be a short treatment course. A treatment that could be taken in just one pill would be the best.

Q What is unique about DSM265?

From the phase I data it looks like it may have potential to be part of a single-exposure treatment. So if this is proven, it would be a good alternative for our patients, especially here in Iquitos where adherence is an issue.

Q What is special about this study?

It's been very interesting to work with a new drug. It's a challenging and complex study, but I have been impressed with the accomplishment of the team. When the weather conditions allow, recruitment in general is not a problem and people are usually happy to participate in the study because malaria is a big problem here and by being part of the trial they know they will receive treatment. Also, we have established a good working relationship with the community. ●

MMV048

is a novel antimalarial compound from the aminopyridine class, and the first new medicine to be discovered by an African-led team. In 2014, it entered phase I. This is the first time a new antimalarial has entered volunteer studies in Africa. MMV048 is highly potent against the blood-stage of malaria – active at doses of less than 100 mg, so at this stage it appears to be at least 10-fold more potent than many medicines used today. As such, it could be a really important part of a single-exposure cure. The compound also has activity against other stages of the parasite lifecycle and all known resistant strains of the parasite, suggesting a role in malaria control, transmission blocking and eradication.

The phase I safety study is being conducted at the University of Cape Town (UCT), South Africa, led by Dr Phumla Sinxadi and Prof. Karen Barnes in collaboration with the South African Technology Innovation Agency.



Dr Phumla Sinxadi
Clinical Pharmacologist at UCT and Lead Investigator for the MMV048 study, explains the goal of phase I studies and how MMV048 is progressing.

Q What is the goal of phase I studies and what do they involve?

The goal is to evaluate the safety and tolerability of the novel compound, in this case MMV048, in healthy volunteers. The first of these studies is known as the 'first-in-human study'. We invite healthy volunteers to participate, by placing adverts in local newspapers – and others hear about the study from past participants. We then screen them to see if they are suitable to be part of the trial. We have screened more than 200 volunteers and dosed 40 subjects, eight of whom have returned for repeat dosing.

Q What factors contributed to the successful completion of the phase I study by UCT?

We have quite a supportive environment with guidance from the UCT human research ethics committee, Triclinium CRO and the South African Medicines Control Council. We also have an international panel of safety experts that look at all the results after each dose before we continue to the next. Its early days, but the good news is that there are no major safety concerns to date.



Prof. Karen Barnes
Clinical Pharmacologist at UCT and Principal Investigator of the phase I trial of MMV048, describes why the compound and development programme are unique.

Q What is unique about the development programme for MMV048?

We are at a very exciting phase with MMV048, as this is the first antimalarial compound researched in Africa to progress to phase I clinical trials. Although we have conducted a number of other phase I studies, this is the first time that our group has taken on a first-in-human study.¹ Malaria is highly prevalent in Africa, so it's important to study new drugs as early as possible in African populations. We are committed to this research.

Q What is MMV's role in this programme?

MMV plays a pivotal role. They bring with them 15 years of experience in developing better and new treatments for malaria. I don't think either UCT or the South African Government would have felt as confident undertaking this kind of study without MMV's technical support. MMV has also been a major co-funder with the South African Government's Technology Innovation Agency. ●

¹ Phase I trials include a series of studies conducted in healthy volunteers to determine the safety of the molecule, the first of which is known as the 'first-in-human study'.

“ I don't think either UCT or the South African Government would have felt as confident undertaking this kind of study without MMV's technical support. **”**



Developing a single-exposure cure to stop the relapse

Tafenoquine

Patient confirmatory (phase III)

Target indication: prevent relapse of *P. vivax*

Key feature: Potential for a single-exposure cure to ensure better patient adherence to treatment

Project Leader: Dr JP Kleim, GSK, UK

MMV Project Director: Dr Wiweka Kaszubaska

ISSUE

Relapsing *Plasmodium vivax* malaria is estimated to cause around 70–80 million clinical infections every year.¹ Primaquine, the only widely available medicine to prevent the relapse of *P. vivax* malaria, has been in use for 60 years and the 7–14 day treatment regimen proves difficult for patients to comply with in clinical practice.

ACTION BY MMV AND PARTNERS

MMV is working in partnership with GSK to develop tafenoquine, a single-exposure anti-relapse medicine. GSK is also working with the Foundation for Appropriate Technologies in Health (PATH) to develop a new diagnostic.

Tafenoquine is currently in phase III development with GSK. The aim is to investigate its potential as a single-exposure medicine to prevent the relapse of *P. vivax* malaria, with the current intention of submitting a new drug application to the US FDA² in 2017. If successful, it would be the first new medicine for relapsing malaria to progress to regulatory approval in over 60 years. Tafenoquine would be used alongside a blood-stage medicine, which together would cure the current malaria infection and prevent a future relapse.

Tafenoquine is an 8-aminoquinoline from the same chemical family as the current standard of care, primaquine. This class of drugs is associated with haemolytic side-effects in patients deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD). To ensure tafenoquine is well tolerated by patients, they will need to be tested for G6PD deficiency before treatment – as they should be today before taking primaquine.

GSK is working with PATH to accelerate the development of a G6PD point-of-care test.

¹ Mendis K *et al.* "The neglected burden of *Plasmodium vivax* malaria." *Am J Trop Med Hyg.* 64 (1–2 Suppl): 97–106 (2001).

² US FDA: United States Food and Drug Administration.



Penny Grewal-Daumerie
MMV's Director, Access and Delivery, and MMV access lead for tafenoquine, explains the excitement around the potential new medicine and the plan to ensure patient access if approved.

Q What is exciting about tafenoquine, for you and the malaria community?

As a single-exposure cure, tafenoquine could potentially overcome the compliance issue of a 7- or 14-day course and revolutionize the treatment landscape for relapsing malaria. It would provide countries with an effective tool to tackle the *P. vivax* hypnozoite reservoir, thereby reducing transmission and the overall disease burden. This would pave the way for elimination. As patients will be screened for G6PD deficiency before receiving tafenoquine, health-care providers will have greater confidence in treating their patients.

It is a privilege to work with GSK on an access strategy for a medicine that we hope will meet a real unmet need.

Q What's involved in the process of ensuring patient access to tafenoquine?

Tafenoquine is a fairly complex proposition as it entails the adoption and roll-out of two products – a G6PD test and the medicine itself. That makes access planning all the more challenging!

Before we could develop an access strategy for tafenoquine we needed a whole range of information including *P. vivax* epidemiology, how the disease is managed, why countries do or do not implement a radical cure, G6PD prevalence, views on testing, supply chain issues etc. To get this information, we conducted market and desk research, and held consultative meetings with experts, policy-makers, malaria-control programme managers and other stakeholders. This provides the basis for the joint access and delivery strategy being developed by MMV, GSK, PATH and the Bill & Melinda Gates Foundation to help ensure timely access to a safe and effective radical cure.



Rithsankan's story, Cambodia

Rithsankan Kea Kim lives with his wife and two sons in Oslev, a small mountain village in Cambodia, close to the Thai border. He farms soya beans for a living. In 2014, he suffered from malaria five times; twice it was caused by *P. vivax* and three times it was a mixed infection. "I feel pain in my whole body, in my bones too," said Rithsankan.

In Cambodia, ACTs are used as first-line treatment for the blood stage of uncomplicated malaria caused by all species of parasite.³ In view of concerns over G6PD deficiency in the country,⁴ primaquine is currently not routinely used to prevent the relapse of *P. vivax*.

Suffering from malaria repeatedly takes its toll on individuals, families and the community. "When I have malaria I can't make any business to support my family. I am the head of the family and so my wife and children rely on me," said Rithsankan.

"They can't go to the field either, as they need to look after me. It takes me a long time to recover. After the treatment I am weak. I wish for a treatment that I could take just once."



³ National Treatment Guidelines for Malaria in Cambodia (accessed May 2015): <http://whothailand.healthrepository.org/bitstream/123456789/1442/1/NTG%20in%20English-Final.pdf>

⁴ Howes RE et al. "G6PD deficiency prevalence and estimates of affected populations in malaria endemic countries: a geostatistical model-based map." *PLoS Med.* 9(11): e1001339 (2012).



Richard Rankin
Global Marketing Director, Infectious Diseases, GSK, explains the key challenges that must be overcome to support optimal use of tafenoquine in malaria-endemic countries, if approved.

Q What are the specific challenges involved in ensuring patient access for tafenoquine?

One of the biggest challenges is managing the possibility of haemolysis in patients that are G6PD deficient. Before tafenoquine administration, patients will need their G6PD levels tested to ensure tafenoquine is used safely and effectively. Right now no suitable quantitative G6PD tests are available for reliable use in the field. GSK is collaborating with PATH and diagnostic developers and a prototype device is already being tested in the laboratory. One of the biggest challenges in terms of implementation will be to ensure the medicines and tests are available together.

Q How is the team working to overcome these challenges?

By working in partnership. We are collaborating with MMV, PATH and the Gates Foundation to co-create a patient access plan. This includes

thinking through how tafenoquine and a G6PD-deficiency test could be introduced in close consultation with malaria-control programme managers, experts and WHO.

I think one of the biggest achievements in terms of access planning for tafenoquine has been obtaining the input of several partners at an early stage to develop a comprehensive plan. We believe this plan will support the success of the programme.

Q What are the next steps to ensure patient access should tafenoquine receive stringent approval?

Once tafenoquine and a point-of-care test have been approved for use, we will continue to work in partnership and solicit greater involvement from the malaria community. GSK and MMV are developing this medicine to meet the needs of populations afflicted by *P. vivax* malaria. Our objective is to have tafenoquine widely available and

affordable in malaria-endemic countries. That's what is driving us. GSK intends to provide the medicine at an affordable price to enable wide patient access in these countries.

It's absolutely critical that once we have filed an application for tafenoquine for regulatory approval, we work more closely with affected countries to see how we can support their implementation efforts. For this to succeed, it needs to be driven by the national malaria-control programme managers.

Q What has it been like to work with MMV on access planning for tafenoquine?

We really value the contribution that MMV makes in terms of partnership and contacts with policy-makers at both the global and regional level. The knowledge, expertise and links MMV has with the wider malaria community are unique. ●



4

Advancing the science of eradication

Discovering new molecules to prevent relapse

ISSUE

Relapsing malaria is estimated to cause around 70–80 million clinical infections every year.¹ The only two medicines known to stop the relapse, (one available and one in development), are from the 8-aminoquinoline family and associated with side-effects in glucose-6-phosphate dehydrogenase (G6PD) deficient patients.

ACTION BY MMV AND PARTNERS

Develop and employ assays to discover new molecules that could stop the relapse given their demonstrated activity against the liver-stage of *P. vivax* malaria.

¹ Mendis K *et al.* "The neglected burden of *Plasmodium vivax* malaria." *Am J Trop Med Hyg.* 64 (1-2 Suppl):97-106 (2001).

To identify safe, new molecules active against the dormant liver-form (the hypnozoite) of *Plasmodium vivax* and *P. ovale*, MMV has a pragmatic test cascade in place. Large numbers of compounds known to be active against blood-stage parasites are screened first in an *in vitro* liver-stage assay, using rodent (*P. berghei*) or simian (*P. cynomolgi*) parasites, to determine if they have activity against liver-stage schizonts and hypnozoites (see Fig 1). Active compounds are then progressed to an *in vivo* assay to confirm their activity against the hypnozoites in a more physiologically relevant model.

The limitation of the current test cascade, however, is that we are not testing against parasites that infect humans (*P. vivax* and *P. ovale*) and so might miss some molecules. Additionally, the throughput of current assays looking at the *P. cynomolgi* hypnozoite is limited. To overcome this, MMV and the Bill & Melinda Gates Foundation (BMGF) are working with different research groups to develop a cost-effective *P. vivax* liver-stage assay.

In a major step towards that goal, a team of researchers from Mahidol University, Thailand, has now developed a *P. vivax* 'hypnozoite' cell-based *in vitro* assay able to screen up to 150 compounds a year.



Dr Jetsumon Sattabongkot
Head of the Mahidol Vivax Research Unit, explains how the assay works, what it reveals and what lies ahead.

Q What was involved in setting up the hypnozoite assay?

One of the issues with studying vivax and setting up an assay is that the blood-stage parasites can't be cultured continuously *in vitro*. So you need to have access to new parasites, and therefore patients, on a regular basis. In Thailand,

we have both main species of parasite – *P. falciparum* and *P. vivax*, so we are well situated for this kind of research. We have been able to develop *P. vivax* liver-stage cultures *in vitro* successfully for up to 4 weeks. This timeframe is in line with the typical time to relapse in Thailand.

The Center for Infectious Disease Research, formerly Seattle Biomed, a research institute in the USA, has recently developed reagents especially for vivax, enabling us to specifically identify the developing parasites in human cell lines. This really opened the door for more vivax research.

Q How does the assay work?

We culture human hepatoma cell lines (HC-04) in an 8-well plate. One day later we add *P. vivax* sporozoites into each well. The sporozoites come from mosquitoes from our insectary that have been fed on patient blood. We add the compounds to be investigated into the vivax cultures in triplicate wells and at a range of different concentrations, keeping some wells without compound as the control. Two weeks later, we count the small and large parasite forms, take the average and compare them with the control wells.

With this assay we can perform two types of experiment. In the first, we mix the drug with the liver cells before – or at the same time – as the sporozoites are added and this allows us to study

the chemopreventive ability of the compounds. In a second experiment, we add the compounds several days after addition of the sporozoites to the liver cells, allowing us to look at the ability of the compounds to kill hypnozoites.

Q Which compounds have you screened so far and what did you find?

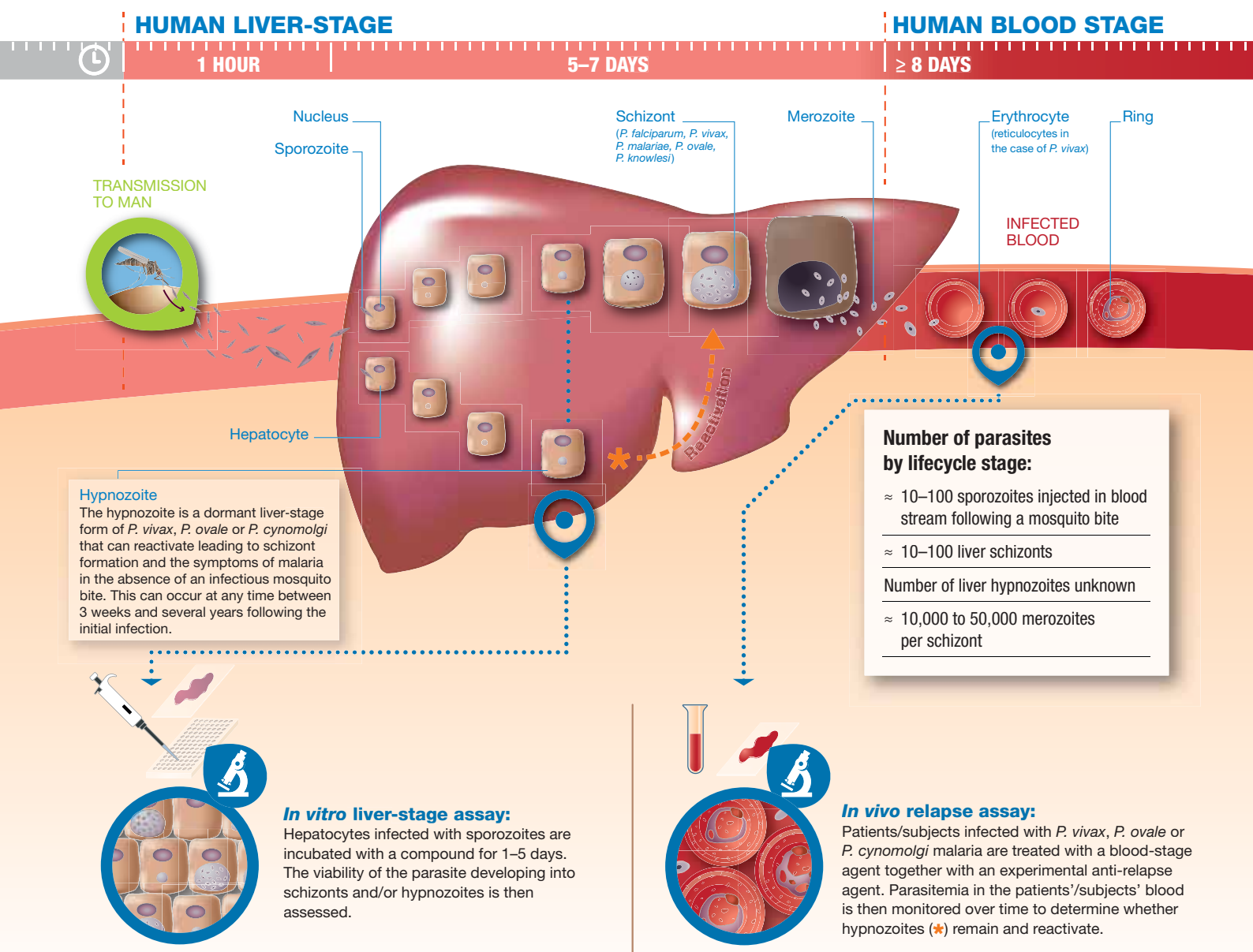
The assay has been validated with primaquine and atovaquone as controls, to ensure it was working. We have also begun testing six out of 10 compounds from MMV's portfolio. All the MMV compounds tested showed efficacy against the small forms in the prophylactic assay confirming the data obtained previously in the surrogate assay using *P. cynomolgi*. Interestingly, one of the compounds that was found to be weakly active in this assay

was found to be highly active in the *P. vivax* liver-stages assay. This tells us that using this assay we are able to detect false negatives that would be missed by the *P. cynomolgi* assay.

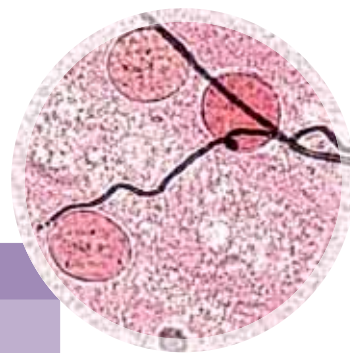
Q What has it been like working as part of the BMGF liver-stage consortium?

It has increased our ability to study the liver-stage parasite. By collaborating with other scientists, including those at MMV, we can access new tools and reagents for parasite identification and contribute *P. vivax* sporozoites to the group – a critical component of all experiments proposed by the consortium. Thanks to the generous support of the BMGF, by working together, every group in the consortium is able to move forward faster. ●

Figure 1: Malaria liver-stage biology and assays to identify compounds to kill it



Identifying new transmission-blocking agents



Oocysts in the mosquito midgut

ISSUE

The lifecycle of the parasite in man and mosquito perpetuates transmission and disease. One way to break the transmission cycle is to have medicines that kill the gametocytes or sexual stages, and so prevent patients from re-infecting mosquitoes.

ACTION BY MMV AND PARTNERS

Develop and employ assays and innovative technologies to discover and develop new molecules to block malaria transmission, and prioritize the pipeline accordingly.

Several of the molecules progressing through clinical development and translational research have demonstrated that they can kill the sexual stages or the gametocytes *in vitro*. Over the last year using a Standard Membrane Feeding Assay (SMFA) in collaboration with scientists at TropiQ in the Netherlands and GSK in Spain we have shown that many of these molecules also have the potential to block the transmission of malaria in the laboratory (OZ439,¹ KAE609,² KAF156, DDD498, SJ733, PA92 and GSK030). The assay works by allowing mosquitoes to feed on malaria-infected blood cultured *in vitro*, combined with a compound and then dissecting the mosquitoes to see if the parasite was able to develop. This assay has enabled us to rank compounds in terms of activity.

To verify this activity clinically, we have two approaches. First, with the Ifakara Health Institute in Tanzania, MMV has established an insectary and proof-of-concept transmission-blocking model using the SMFA, but where mosquitoes feed on blood from study participants treated with a test drug, under very carefully controlled conditions. We are currently validating this model with the standard treatment regimens of artemisinin combination therapy and a single low dose of primaquine.

Second, we are working with the QIMR Berghofer Medical Research Institute in Queensland Australia to adapt the Controlled Human Malaria Infection Model (page 13) to assess transmission-blocking capabilities. During the original studies, we observed that certain drugs, e.g. piperazine phosphate, increase the number of gametocytes in the bloodstream. Building on this, we plan to investigate the transmission-blocking capabilities of molecules such as OZ439 and KAE609 in 2015. The model has been validated using a single dose of primaquine, as recommended by WHO. In parallel, we can use membrane feeding assays to see if the remaining gametocytes are actually able to develop in the mosquito.

In addition, in collaboration with the Bill & Melinda Gates Foundation, the hunt continues for new transmission-blocking chemical scaffolds. We can carry out high-throughput screens against the gametocytes themselves and find compounds capable of killing both these and the normal blood stages. However, what would be really useful is to have a complete transmission-blocking assay for *P. falciparum*. The biggest challenge is that the current assay (SMFA) is very labour intensive and therefore time consuming. Working with TropiQ and with GSK, we have increased the efficiency of the assay and therefore the number of molecules that can be analyzed.

- 1 Delves M *et al.* "The activities of current antimalarial drugs on the life cycle stages of *Plasmodium*: a comparative study with human and rodent parasites." *PLoS Med.* 9(2):e1001169 (2012).
- 2 van Pelt-Koops JC *et al.* "The spiroindolone drug candidate NITD609 potentially inhibits gametocytogenesis and blocks *Plasmodium falciparum* transmission to anophelous mosquito vector." *Antimicrob Agents Chemother.* 56(7):3544-8 (2012).
- 3 Biosafety level: level of the biocontainment precautions required to isolate dangerous biological agents in an enclosed laboratory facility. The levels of containment range from the lowest biosafety level 1 to the highest at level 4.

Q What were the challenges you faced in setting up the assay and how did you overcome them?

One of the key challenges is ensuring the results remain robust and reproducible. We have a highly efficient and well trained team of people and have standardized our protocols to obtain an efficient parasite read out in the mosquito, enabling us to screen around 40 molecules per year.

A key priority when working with infected mosquitoes is biosafety – we need to ensure no infected mosquitoes escape. The insectary at GSK is a Biosafety Level 3³ facility, which means we are extremely careful about this.

Another challenge is to keep the mosquito breeding environment as close to real life as possible. In industry, we work in extremely clean and sterile environments and we observed that from generation to generation the mosquitoes lose their natural bacterial flora – even mosquitoes have bacteria in their guts just like you and I. This flora is actually important for transmission. We have now changed the breeding protocol to make it more realistic.

Q How many molecules have you been able to analyze and what did you find?

So far, we have analyzed 40 molecules, 15 of which have been fully profiled, meaning that we have assessed them in different concentrations to understand the

dose and response relationship. Some molecules are extremely promising and are in clinical development, for example, OZ439 and KAE609. GSK assets like the dione, thiotriazole and aminoindole series have also shown transmission-blocking potential in the assay. GSK030 from the thiotriazole series was declared a preclinical candidate in 2014. This is something we are really excited about.

We also want to increase the efficiency of the assay by decreasing the number of mosquitoes per assay, as well as minimizing the labour intensive mosquito dissections and parasite counting post-infection. We are looking at several options. Lots of progress is being made so it's an exciting time to be involved! ●



Dr Janneth Rodrigues
Insectary Supervisor at GSK-Tres Cantos, explains her work to establish the assay in an industrial setting.

Finding new ways to protect women and children

ISSUE

Medicines currently used to protect vulnerable populations are becoming less effective as the parasite develops resistance; they are also often not well tolerated. Moreover, as the burden of malaria declines, immunity will decline. These factors increase the need for new protective medicines.

ACTION BY MMV AND PARTNERS

Develop tools and screen compounds to identify novel molecules with prophylactic activity.

For a compound to have prophylactic potential it ideally needs to act against the early lifecycle stages of the parasite – the sporozoites from the mosquito bite and the dividing form in the liver, known as schizonts. By targeting these forms we can stop asexual blood-stage parasites, which cause the clinical symptoms of malaria.

MMV is working with the University of California, San Diego (UCSD), to screen compounds for activity against these forms using a rodent parasite (*P. berghei*). The team has successfully optimized the assay and screened over half a million compounds in the last year, identifying hundreds of active compounds. They are now analyzing the data.



Dr Elizabeth Winzeler
University of California, San Diego, talks about the importance of continuing the hunt for new molecules and the collaboration with MMV.

Q Why do we need to identify new molecules active against the liver and other stages of malaria?

A lot of the medicines we have, like quinine and artemisinin, were developed from natural products. They were never really designed to get rid of all the stages of the parasite in the body; they were designed to make you feel better. Today, we have a much deeper understanding of the role of various stages of the parasite's lifecycle leading to transmission and relapse, which means we can really design 'so called' sterilizing medicines that could eliminate all the stages in the lifecycle. It's a high hurdle, but I think we can do it.

Q How does the assay work?

We receive mosquitoes carrying rodent malaria. The parasites are treated with a specialized luciferase marker, which means they output light.

We dissect the mosquitoes and put them onto a lawn of liver cells treated with compounds.

If the compound has no effect they invade and develop a productive

infection in the cells. The parasites will then convert luciferin to light. We can detect compounds that prevent this from happening based on the light output from our screening wells. We can screen large numbers of compounds in this way.

Q What have you found so far?

We are currently analyzing the data from the set of 550,000 compounds provided by MMV that we recently screened. Previously, we screened about 100,000 compounds from different libraries from MMV's partners. Of these, we performed a dose-response analysis of 10,000 compounds.

We have at least 2,000 compounds with promising activity at appropriate concentrations that we will follow-up. Seven hundred are very potent and might be interesting for further development.

Q What are the next steps?

The same compounds have also been screened in a blood-stage assay. The data sets will be analyzed together and the compounds prioritized for testing in specialized assays. We're also interested in testing the most

Prioritizing molecules that are well-tolerated by pregnancy

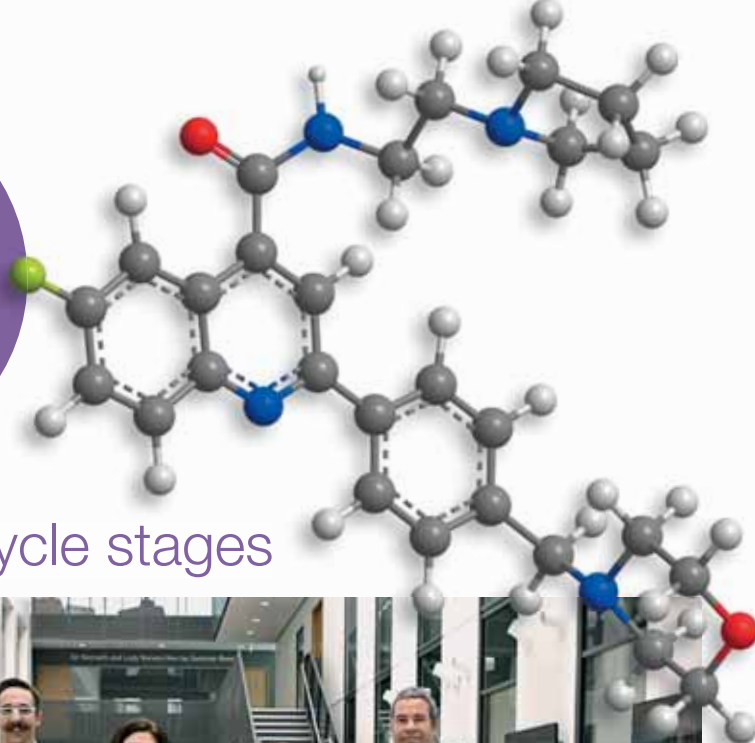
There is a large call for medicines which are well-tolerated in pregnancy (see page 30). Traditionally, pre-clinical studies to determine if a molecule could be considered as such are conducted in parallel with phase II studies. MMV is now routinely doing them in parallel with phase I (as was the case for MMV048, pages 16–17) and looking at doing them even earlier. In this way, we ensure that medicines which could protect vulnerable populations are identified early on and prioritized for further development.

promising compounds for activity against gametocytes for transmission blocking and the hypnozoite for radical cure. I expect at least a subset of these compounds would have what I like to call 'sterilizing activity' so they would eliminate hypnozoites as well as the transmission and blood stages. While we're not 100% clear how to identify this magical compound, we are taking a pragmatic approach to screening compounds in a sequence of assays to identify which could serve as scaffolds for drug discovery efforts. ●

“We have at least 2,000 compounds with promising activity at appropriate concentrations that we will follow-up.”

MMV
Project
of the Year
2014

DDD498



One molecule: multiple lifecycle stages

DDD498

Preclinical

Target indication:

Part of a combination treatment for acute uncomplicated malaria

Key features:

- Potential for a single-exposure treatment in combination with a partner drug
- Novel mechanism of action – inhibiting the parasite elongation factor (EF2)¹
- Comparable activity across multiple stages of the malaria parasite lifecycle including inhibition of development of all liver stages (important for chemoprevention) and outstanding transmission-blocking potential

Discovery Project Leaders:

Prof. Ian Gilbert and Dr Kevin Read,
Drug Discovery Unit, University
of Dundee, UK

MMV Project Director: Dr Paul Willis



The team at Dundee University Drug Discovery Unit (DDU).

This molecule has caused a stir among researchers the world over. DDD498 has potent activity against multiple stages of the malaria parasite's lifecycle, giving it the potential to cure and stop the spread of the disease as well as protect people, all in a single-exposure.

The compound was identified in partnership with the University of Dundee's DDU, and draws on expertise from MMV's global network of scientists. Working in a completely different way to other antimalarial medicines,¹ it targets and inhibits part of the machinery that synthesizes proteins within the parasite. Unable to make proteins, the parasite cannot survive.

In recognition of the molecule's promise and the dedication of the team at the Dundee DDU, the project has been named MMV Project of the Year 2014. Project Leaders Prof. Ian Gilbert, Head of Chemistry (seated, 3rd from the right), and Dr Kevin Read, Head of Drug Metabolism and Pharmacokinetics (seated, 3rd from the left), will receive the award at MMV's Expert Scientific Advisory Committee (ESAC) meeting in July 2015 in Tokyo, Japan. They explain how the discovery was made and their experience of working with MMV.

“It has been a very open collaboration – a true partnership. It's been extremely valuable on many different levels...”

Q How was the compound discovered?

At Dundee's Drug Discovery Unit we have a strong interest in neglected tropical diseases. So when MMV approached us to test one of our compound libraries against the malaria parasite, we were happy to participate. A total of 4,700 compounds were screened, giving us 11 active chemical series. MMV was already working on some of them. We began chemistry work on four series that no one was yet researching. After several cycles of design, compound preparation and testing, we identified DDD498 from one of the series.

Q What were the biggest challenges you faced and how did you overcome them?

The compounds were very much early-stage hits when we began working on them. Much of the early work focused on improving the characteristics of the molecules to make them more drug-

like. For example, one of the challenges we had to overcome was that the early leads had poor membrane permeability, meaning that as drugs they would be poorly absorbed in the body.

We also needed to improve the activity of the compounds against the parasite that causes malaria. As with any compound from a phenotypic screen,² you do not know how it is binding to its target, so there's always the challenge of understanding which is the best way to optimize the compound.

To overcome the challenges, we had a very focused campaign; we were strict about what we made in terms of chemistry and used a series of assays to eliminate compounds that would not make the cut.

Q What has it been like to work with MMV on DDD498?

It has been a very open collaboration – a true partnership. It's been extremely

valuable on many different levels: first of all, having regular interactions with the team at MMV, particularly Dr Paul Willis and Sir Simon Campbell's advice on which assays and experiments to conduct, and to really question what we were doing. Second, having access to the assays for the different stages of the lifecycle that MMV has put in place was essential for understanding the properties of the compounds.

Most importantly, MMV brought focus to the project. MMV's target product profiles, target candidate profiles (pages 8–9) and progression criteria have been really critical in guiding what we have done. It's a well thought out process of what you really need to do to develop a compound, and accelerates the research process in a focused way, while ensuring critical questions are answered.

Without all of this, it would have been very lengthy and challenging to get to where we are today.

- 1 Baragaña B *et al.* "A novel, multiple-stage antimalarial agent that inhibits protein synthesis." *Nature* 522, 315–320 (2015).
- 2 Phenotypic screen: compounds are tested for their activity against the whole parasite to identify those that cause the desired biological change, in this case parasite death.
- 3 Controlled Human Malaria Infection Model: enables candidate medicines to be tested for blood-stage activity in volunteers inoculated with a small dose of malaria in a tightly controlled environment.



Dr Paul Willis
Director, Drug Discovery at MMV, and Project Director for the discovery of DDD498 explains how the team came together to discover the compound.

Q Who were the key partners in the discovery and research of the compound?

The core team involved scientists from the DDU, University of Dundee, working in collaboration with MMV. Dundee has built an academic unit that combines medicinal chemistry, biology and drug metabolism. There are very few academic institutions that integrate these core areas of expertise needed for drug discovery. Working with such a multi-skilled team certainly helped the project to progress quickly.

Leading malaria researchers from MMV's global network also contributed in various ways, for example, when it came to testing the compound against the various stages of the parasite's lifecycle. In particular, the whole team benefited greatly from the vast drug discovery experience of Sir Simon Campbell, a member of MMV's ESAC. Also, contributions from Prof. Julian Rayner of the Wellcome Trust Sanger Institute and Prof. David Fidock of Columbia University were instrumental when it came to understanding the novel mechanism of action.



Dr Lidiya Bebrevska
Associate Director, Translational Medicine and MMV Project Director for the translational research phase of DDD498 summarizes recent progress and the next steps.

Q How is the project progressing and what are the next steps?

In 2013, MMV selected DDD498 to enter preclinical development, following recommendation from ESAC. Since then, MMV has been conducting a series of translational activities to progress the compound to early clinical studies in humans. First, ensuring we have sufficient volume of the compound as a drug product of quality suitable for clinical use. Second, ensuring there are no toxicity issues prohibiting dosing in healthy volunteers and estimating the safety limits in humans. Third, planning to start phase I studies and the work on the Controlled Human Malaria Infection Model in Queensland in 2016.³

In addition in 2014, MMV's business development team worked on identifying a development partner for this project, a company to work with MMV and take the project forward through clinical development. ●

5

Saving more lives with current medicines



Saving Precious, Nigeria



"On Sunday 3rd of May, 2015, Precious started vomiting and had diarrhoea. He had a high temperature and within a short time became very weak. I had to rush him to the hospital. I was so afraid that I left him in God's and the doctors' hands," said Mrs Bosede Adebayo, whose son, 11-month-old Precious, was admitted to the General Hospital Okeho, Ibadan, Oyo State, Nigeria, on confirmation of severe malaria.

The first dose of injectable artesunate (Artesun® 60 mg, manufactured by Guilin Pharmaceutical) was immediately administered and after 3 days Precious was well enough to be discharged.

"The response to treatment was very encouraging and amazing," said Dr Olusola Ayeleke the treating physician. "Precious responded quickly. Following the first dose there was significant improvement and by the time the second and third doses had been administered, he began eating well, taking oral medications and was good to go."

Dr Ayeleke attributed the positive outcome to the use of injectable artesunate provided to the hospital through the Improving Severe Malaria Outcomes (ISMO) project, supported by UNITAID, MMV and the Malaria Consortium in collaboration with the Oyo State Government. "Before the MMV-led ISMO project, treating severe malaria was really challenging because we were using intravenous quinine," said Dr Ayeleke. "There was increased mortality due to malaria. Intravenous quinine is associated with side effects and must be administered more frequently. Injectable artesunate makes the management of severe malaria easier and more fruitful."

"After the ISMO training, health workers can use injectable artesunate to treat severe malaria patients," said Dr Campbell Ibijoke Oluyomi (pictured on the left), the Consultant Paediatrician in charge of Oni Memorial Children's Hospital. "It is very fast acting and so patients recover from the condition faster and are no longer dying from severe malaria."

Supporting the switch, saving more lives

Injectable artesunate¹

WHO prequalified product
(manufactured by Guilin Pharmaceutical)

Indication: Severe malaria

Potential impact: 22.5% reduction in mortality in Africa² and a 34.7% reduction in Asia³ compared to previous standard of care (quinine)

Implementing partners: Clinton Health Access Initiative (CHAI), Malaria Consortium (MC) and Swiss Tropical and Public Health Institute (Swiss TPH)

MMV Project Director: Pierre Hugo

Since Guilin Pharmaceutical became the first company to receive WHO prequalification for their injectable artesunate, Artesun®, in 2010, over 36 million vials of the medicine have been delivered to malaria-endemic countries (as of May 2015). Given that artesunate injection offers a 22% reduction in mortality compared to the alternative, injectable quinine,² an estimated 200,000–240,000 additional lives have been saved during that time.

ISSUE

Lack of access to injectable artesunate – the WHO-preferred treatment for severe malaria – costs lives. Countries need support to make the switch to this drug from quinine, the current standard of care.

ACTION BY MMV AND PARTNERS

Develop multi-stakeholder consensus and roadmap to support the switch and provide support and funding to make it a reality, including:

- ➔ Early-stage evaluation and introduction studies in the Democratic Republic of the Congo (DRC) and Nigeria
- ➔ Mobilize donor funding for scale-up in six high-burden countries to support training and procurement
- ➔ Secure new generic manufacturers to increase drug supply



While uncomplicated malaria is debilitating, when it progresses to severe malaria it becomes deadly. Around 584,000 people die each year of severe malaria, 75% of whom are under the age of 5.⁴ Since 2011, WHO recommends injectable artesunate as first-line treatment for severe malaria, as it saves more lives than quinine.^{2,3}

To improve access and increase use of the medicine across the malaria-endemic world, MMV joined forces with two partners with global reach: first with CHAI in Nigeria to support the introduction of the medicine⁵ and then Swiss TPH in the DRC to gather evidence to support the switch. These two countries together represent around 30% of the global population at risk of malaria.⁴

The DRC has the highest burden of severe malaria in the world. In 2013 and 2014, MMV, Swiss TPH and the Kinshasa School of Public Health collaborated with the National Malaria Control Programme to undertake a study comparing injectable artesunate with quinine in four districts in and around Kinshasa. The study reported 3.8% case fatalities with quinine and 1.7% with artesunate, with a median time to discharge of 3 versus 2 days, respectively.^{6,7}

These findings supported the inclusion of injectable artesunate into the DRC's strategic plan and a request for funding to the Global Fund. As a result, national deployment of injectable artesunate will take place in the DRC over the coming years. The target is for all reported severe malaria cases to be treated with the medicine by 2016–2017.

Based on the knowledge and experience gained in Nigeria and the DRC, MMV established a severe malaria consortium with CHAI and MC. In 2013, this MMV-led Improving Severe Malaria Outcomes (ISMO) project was awarded a UNITAID grant of USD 34 million to continue the scale-up of injectable artesunate in 13 of the 36 states in Nigeria and in five other high-burden African countries (Cameroon, Ethiopia, Kenya, Malawi and Uganda).

To ensure injectable artesunate is used correctly, appropriate and timely training is critical. Through the ISMO project, MMV and partners have benefited from the experience of Médecins Sans Frontières to train health-care workers in the use of the drug. To date, health-care workers in 1,175 facilities (as of 31 December 2014) across the six countries have been trained – exceeding the total target number for the project (1,039).

To continue the scale-up we must also ensure supply can meet demand. Working with the President's Malaria Initiative and the Global Fund is critical to ensuring accurate quantification and forecasts. Should all reported cases of severe malaria be treated, it is predicted that 40–60 million vials of injectable artesunate will be needed worldwide each year. Yet, today only 11–12 million vials are manufactured annually. The ISMO project seeks to reduce this supply gap by helping to introduce new manufacturers. This will help secure uninterrupted access to high-quality and affordable supplies. ●

- 1 Late onset haemolysis has been reported with the use of injectable artesunate. Published reports recommend that treatment with injectable artesunate should be limited to the required period and followed by a full course of an oral antimalarial, in line with WHO recommendations. Monitoring for late haemolytic anaemia should occur in all cases of severe malaria, irrespective of treatment.
- 2 Dondorp AM *et al.* "Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial." *Lancet*. 376(9753):1647-57 (2010).
- 3 Dondorp A *et al.* "Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial." *Lancet*. 366(9487):717-25 (2005)
- 4 World Health Organization. World Malaria Report 2014: http://www.who.int/malaria/publications/world_malaria_report_2014/en/
- 5 Medicines for Malaria Venture Annual Report 2013, Chapter 3 "Expediting access to approved medicines", p 16: http://www.mmv.org/sites/default/files/uploads/docs/publications/annual_report_2013/Annual_Report_2013_Chapter_3.pdf
- 6 Burri C, Hugo P, Poll E & Tshetu A. "Saving more lives from severe malaria." *Africa Health* pgs 32-33 Sept (2014): http://www.africa-health.com/articles/november_2013/MMV.pdf
- 7 Ferrari G *et al.* "An operational comparative study of quinine and artesunate for the treatment of severe malaria in hospitals and health centres in the Democratic Republic of Congo: the MATIAS study." *Malar J*. 14(1):226 (2015).



Buying time for severe malaria treatment

Rectal artesunate

Preparing for WHO prequalification

Target indication: Pre-referral treatment for severe malaria

Potential impact: A single suppository substantially reduces the risk of death and permanent disability in children when the time for referral exceeds 6 hours^{3,4}

MMV Project Director: Pierre Hugo

1 World Health Organization. Guidelines for the treatment of malaria. Third edition. April 2015: <http://www.who.int/malaria/publications/atoz/9789241549127/en/>

2 WHO-TDR: World Health Organization Special Programme for Research and Training in Tropical Diseases.

3 World Health Organization. Malaria in children under five: http://www.who.int/malaria/areas/high_risk_groups/children/en/

4 Gomes MF *et al.* "Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial." *Lancet*. 373(9663):557-66 (2009).

5 World Health Organization. Rectal artesunate testing and delivery: http://www.who.int/tdr/research/malaria/rectal_artesunate/en/



ISSUE

WHO Standard Treatment Guidelines for Malaria¹ include the use of rectal artesunate for pre-referral treatment for severe malaria. However, no WHO-prequalified product exists.

ACTION BY MMV AND PARTNERS

With early collaboration from WHO-TDR,² define requirements for WHO-prequalification of rectal artesunate; work with pharmaceutical partners, Cipla and Strides Arcolab, to obtain a prequalified product and optimize its use in low-resource settings.

The first point-of-care for many patients with severe malaria is a community-level health-care worker (CHW) or primary care facility. These critically ill patients should be treated as quickly as possible with injectable artesunate; however, local health posts may not have this drug or trained personnel to administer it. In such cases, WHO recommends the use of rectal artesunate (RAS) as a pre-referral treatment; this option can substantially reduce the risk of death or disability, buying time for patients to be referred to centres that can provide recommended treatment.⁵ However, no WHO-prequalified version of RAS exists, leaving malaria-control programmes and donors without a quality-assured option.

With funding from UNITAID, MMV is working with two Indian pharmaceutical companies, Cipla Limited and Strides Arcolab Limited, to develop RAS for submission to WHO prequalification by the end of 2015 and market introduction in 2016. This process will build on clinical studies led by WHO-TDR, which demonstrated the benefits of RAS.²

MMV has also conducted qualitative research in 20 high-burden malaria countries in sub-Saharan Africa to understand the need, barriers to use and potential market demand for a pre-referral severe malaria treatment. The research revealed which countries are best placed to integrate the product after its prequalification.



Dr Yusuf Hamied
CEO of Cipla Limited, talks about getting involved in developing an RAS product and why they chose to work with MMV.

Q What motivated Cipla to get involved in the development of rectal artesunate?

Cipla has been manufacturing antimalarial drugs since its inception in 1935. We believe that we are among the largest producers in the world of artesunate and artemether, two of the key medicines to treat malaria today. We are also in the process of producing injectable artesunate. Two years ago, we were asked to consider making rectal artesunate as well. We already have an approved facility for making rectocaps and as they have been shown to save lives, for us this project is a priority.

Q Why did you choose to partner with MMV on this project?

MMV is extremely well known for its expertise in malaria and Cipla has been wanting to work with MMV for a very long time. We hope this project will lead to further projects in the area.



Mr Mohan Kumar
CEO of Strides Arcolab Limited, explains how Strides will make a prequalified product widely available and what it is like to work with MMV.

Q What key lessons can Strides bring to ensure RAS becomes more widely available?

Strides has a distribution network in 25 countries across the African region. We have 250 medical representatives and field staff overseeing operations in these countries. Our established presence will accelerate access to the product for patients, once it is prequalified.

Q What's different about this project compared to other development projects in Strides' portfolio?

This project allows us to play an integral role in saving the lives of children who are critically ill with malaria. Working with MMV has been a privilege for Strides and we really value the partnership. The technical expertise and experience MMV has in bringing a product to market in the malaria field makes this an ideal partnership. ●

Spreading the word about ACTs: effectiveness and safety in the real world

ISSUE

With a range of artemisinin-based combination therapies (ACTs) now available, National Malaria Control Programmes (NMCPs) need to know which should be used for their populations.

ACTION BY MMV AND PARTNERS

Generate and disseminate post-approval evidence on the safety and effectiveness of ACTs in the real world versus in a clinical trial setting, to support their optimal use.

Artemisinin-based combination therapies (ACTs) remain the standard of care for uncomplicated malaria. In artemisinin-sensitive regions, these therapies are highly efficacious (with cure rates between 94–99%).^{1,2} Today, WHO recommends five different combinations.³ Since 2008, these have provided countries with a greater selection of treatments to develop national guidelines for first-line, alternative first-line and second-line treatments for malaria. But how well do they work and what is their safety profile in a real world setting? How well are they addressing the unmet medical needs of patients?

In 2011 and 2012, two MMV co-developed ACTs, *Eurartesim*[®] (dihydroartemisinin-piperaquine) and *Pyramax*[®] (pyronaridine-artesunate), were approved and granted positive scientific opinion by stringent regulatory authorities. A paediatric formulation of *Pyramax* is currently undergoing regulatory approval and one for *Eurartesim* will be submitted in 2016. To help guide best treatment practice, MMV is working with partners to study how these medicines may be best used in the real world.

First, MMV and Sigma-Tau provided *Eurartesim* for the INESS⁴ phase IV platform to gather real-life safety and effectiveness data. In clinical trials, the piperaquine component of *Eurartesim* was shown to transiently lengthen the heart's electrical activity. Although this was shown not to have a clinical effect in the trial population, INESS enabled this to be explored in a real-life setting. INESS is a four-country (Ghana, Burkina Faso, Mozambique, Tanzania) research programme to assess ACTs, supported by the Bill & Melinda Gates Foundation. In 2014, INESS evaluated the use of *Eurartesim* in almost 10,000 patients and concluded that it is well-tolerated, and that transient prolongation of the electrical activity of the heart, occurring in some patients, did not appear to be associated with any clinical symptoms.⁵

Second, with EDCTP's⁶ support, MMV is working with Shin Poong Pharmaceutical and WANECAM⁷ on a longitudinal phase IIIb/IV trial comparing the safety and efficacy of repeated use of *Eurartesim* and *Pyramax* with that of currently used ACTs (artemether-lumefantrine [AL] or artesunate-amodiaquine [ASAQ]). This research is particularly important for *Pyramax*, as it was initially given an Article 58 positive opinion from the European Medicines Agency (EMA) in 2012 for one-time-only use. WANECAM is generating new data on the repeated use of *Pyramax* in adults and children. Interim data from the trial shows that *Pyramax* is equally well tolerated and efficacious for repeat dosing as for initial dosing. This data has now been submitted to the EMA to support a change in *Pyramax*'s label to permit retreatment.

MMV has also collaborated with the Drugs for Neglected Diseases initiative (DNDi) and Sanofi in evaluating Coarsucam[™]/ASAQ Winthrop[®]. In Côte d'Ivoire, over 15,000 patients have been treated with ASAQ and closely monitored for rare adverse events (defined as occurring in 1-in-5000 patients). This study is helping to build a more robust safety record to inform national stakeholders about the real-life experience they can anticipate with ASAQ.

Lastly, in May 2015, artesunate-mefloquine (ASMQ), a DNDi-Cipla prequalified product, entered the MMV portfolio. Disseminating the results of recently completed safety and tolerability studies using ASMQ will be a new area of work for MMV.

MMV is proud to generate and disseminate scientific evidence about these important new treatments to help NMCPs decide which ACTs they should use for their populations. ●



- 1 Rueangweeayut R *et al.* "Pyronaridine-artesunate versus mefloquine plus artesunate for malaria." *N Engl J Med.* 366(14):1298-309 (2012).
- 2 Tshetu AK *et al.* "Efficacy and safety of a fixed-dose oral combination of pyronaridine-artesunate compared with artemether-lumefantrine in children and adults with uncomplicated *Plasmodium falciparum* malaria: a randomised non-inferiority trial." *Lancet.* 375(9724):1457-67 (2010).
- 3 World Health Organization. Guidelines for the treatment of malaria. Third edition. April 2015: <http://www.who.int/malaria/publications/atoz/9789241549127/en/>
- 4 INESS: INDEPTH Effectiveness and Safety Studies of Antimalarial Drugs in Africa.
- 5 Baiden R *et al.* "Prospective observational study to evaluate the clinical safety of the fixed-dose artemisinin-based combination Eurartesim[®] (dihydroartemisinin/piperaquine), in public health facilities in Burkina Faso, Mozambique, Ghana, and Tanzania." *Malar J.* 14(1):160 (2015).
- 6 EDCTP: European & Developing Countries Clinical Trials Partnership.
- 7 WANECAM: West African Network for Clinical Trials of Antimalarial Drugs

Protecting pregnant women

ISSUE

125 million pregnant women are at risk of malaria each year and up to 200,000 babies and 10,000 mothers die as a consequence.^{1,2} To protect them, WHO recommends intermittent preventive treatment in pregnancy (IPTp)³ with sulfadoxine-pyrimethamine (SP).⁴ Today, IPTp coverage is very low – only 24% of pregnant women in sub-Saharan Africa receive the minimum dosing.⁵ In addition, SP might one day lose its chemopreventive efficacy to drug resistance.

ACTION BY MMV AND PARTNERS

MMV and the London School of Hygiene & Tropical Medicine (LSHTM) will undertake a safety study in Tanzania testing DHA-PQP as a possible alternative to SP for IPTp. In addition, MMV sponsored the inaugural meeting of the Call to Action for the Scale-up of IPTp in 2014 and is working with partners to advocate for better IPTp coverage.



Dihydroartemisinin-piperaquine (DHA-PQP) is under consideration for use in IPTp. However, the PQP component can lengthen the heart's electrical activity.⁶ Although this transient effect resolves within 1 week without serious consequences in non-pregnant populations,⁷ a new study will verify if it is comparably well tolerated in pregnant women.

Q Of all the ACTs, why was Eurartesim[®] selected for this study?

DHA-PQP is not only curative for malaria, but it also has a very long half-life. This means that it can clear malaria when administered and provide a long preventive window so that if a pregnant woman gets an infective bite a week after dosing, she will still be protected. PQP has been shown to be protective for up to 63 days after dosing; but it could be longer.



Matthew Chico from LSHTM talks about why DHA-PQP (specifically, Eurartesim[®], developed by Sigma-Tau and MMV) was chosen for this study and when the results are expected.

In Africa, DHA-PQP has been shown to be superior to artemether-lumefantrine at preventing further parasitaemia, although both drugs have failure rates less than 5%.⁷

Q When will we have the answer the study seeks to find?

We should have the answer by June 2016. WHO is interested in the results. In July 2015, it will convene an Expert Review Group to discuss, among other topics, the safety of DHA-PQP in pregnancy. The Expert Review Group will make policy recommendations for consideration by WHO. But without the results of our study, it will be difficult to make an unequivocal endorsement of DHA-PQP for use in pregnancy. This is not 'a-nice-to-know' study; it's a 'need-to-know' study. ●



I need more protection from malaria: Angela's story

Angela Kangulumais is a primary school teacher in Zambia. When we met her she was 6 months pregnant with her second child and no stranger to malaria. Just before her first pregnancy, she had nursed a headache for over a week and woke up one morning unable to see properly and walk unaided. With the help of her husband, she went to the local clinic where she was diagnosed with malaria and prescribed artemisinin combination therapy (ACT). Within a day, she felt much better.

For Angela, the need to protect herself from malaria becomes an even greater priority when she is pregnant. Bed nets are one solution. However, Angela explained. "This method alone is inadequate as I can't always be under the net".

Pregnant women at risk of malaria like Angela benefit from IPTp. According to WHO, this highly cost-effective intervention reduces the chances they will contract malaria and their unborn babies will die. With low coverage levels today, IPTp with SP must be rolled out more broadly in regions where it is effective.

In response, RBM's Malaria in Pregnancy working group and WHO launched a Call to Action in 2014 advocating greater uptake. In parallel, the search continues for new regimens to replace SP in the future.



- 1 Dellicour S *et al.* "Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study." *PLoS Med.* 7(1):e1000221 (2010).
- 2 Lives at risk: malaria in pregnancy [Internet]. Geneva: World Health Organization; 2015. <http://www.who.int/features/2003/04b/en/>
- 3 IPTp: administration of a full course of an antimalarial treatment to pregnant women living at risk of malaria after their first trimester and at a minimum of 1-month intervals.
- 4 World Health Organization. Updated WHO Policy Recommendation (October 2012). Intermittent Preventive Treatment of malaria in pregnancy using Sulfadoxine-Pyrimethamine (IPTp-SP): http://www.who.int/malaria/iptp_sp_updated_policy_recommendation_en_102012.pdf
- 5 Chico M *et al.* "Global call to action: maximize the public health impact of intermittent preventive treatment of malaria in pregnancy in sub-Saharan Africa." *Malar J.* 14(1):207(2015).
- 6 European Medicines Agency: Assessment report: Eurartesim[®] (dihydroartemisinin/piperaquine tetraphosphate). 2011: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001199/human_med_0011450.jsp&mid=WC0b01ac058001d124
- 7 Zani B *et al.* "Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria." *Cochrane Database Syst Rev* 1:CD010927 (2014).

Protecting children during the rainy season

Sulfadoxine-pyrimethamine + amodiaquine (SP+AQ)

Higher strength formulation (children aged 12–60 months) received WHO prequalification in October 2014; infant strength is currently under review and received Global Fund Expert Review Panel approval until November 2015, allowing procurement in the interim.

Indication: Seasonal Malaria Chemoprevention (SMC)¹ for children in areas of highly seasonal transmission across the Sahel sub-region²

Potential impact:

- SMC with SP+AQ has been shown to be generally well-tolerated and efficacious, preventing around 75% of malaria episodes²
- Cost-effective³: high-quality SMC drug costs ~USD 1 per season to protect a child from malaria. The cost of inpatient care for a case of severe malaria has been estimated at between USD 12–75⁴

Partners: Guilin Pharmaceutical Co. Ltd. China

MMV Project Director: Adam Aspinall

ISSUE

WHO recommends seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine and amodiaquine (SP+AQ) to protect children in areas of high seasonal malaria transmission across the Sahel sub-region.² Ensuring that sufficient quantities of quality drugs are available and correctly administered poses significant logistical challenges.

ACTION BY MMV AND PARTNERS

As part of the UNITAID-funded ACCESS-SMC consortium,⁵ MMV is supporting the scale-up of SMC in the Sahel sub-region by helping expand the global manufacturing capacity for quality SP+AQ and supporting the development of improved child-friendly formulations.

In some parts of Africa, during the rainy season, more than 60% of malaria cases occur in just 4 months of the year. Around 39 million African children under 5 years of age live in these regions and an estimated 152,000 die from malaria each year.⁶

Initially, MMV was involved in the West Africa Roll Back Malaria SMC working group, which includes malaria-endemic country institutions, malaria-control programme managers and international partners. More recently, MMV has become part of the ACCESS-SMC consortium, which is supporting the implementation and scale-up of SMC in the Sahel region.



Adam Aspinall
Director,
Product Strategy
& Management
explains the role
of MMV and the
implementing
partners.

Q What is MMV's role in the consortium?

In 2013, we began developing an SMC tool kit for countries interested in implementing this life-saving intervention. The tool kit is a training and communication aid. It assists people 'at the sharp end' with the implementation of SMC and has four sections: planning, training, monitoring and evaluation of results, and communicating the importance and implementation of SMC to people and health-care workers on the ground.

Today, we are participating in a major project funded by UNITAID and led by the Malaria Consortium and Catholic Relief Services to scale-up the intervention in the Sahel region. Our role is to make sure that a quality medicine is available, and that there is enough of it at the right time. First, we are working with Guilin Pharmaceutical to obtain

WHO prequalification for both strengths of SP+AQ and develop a child-friendly formulation, which should significantly improve the ease of administering the treatment. Second, to secure the drug supply, we are identifying additional manufacturing capacity for prequalified SP+AQ.

Q What is the role of the implementing partners?

The implementation of SMC is a complicated logistical process. The implementing partners are working at the frontline to ensure the medicine is administered appropriately to the children that need it. They must work closely with national government partners to ensure that community-based delivery of monthly treatment can effectively be managed for up to 4 months in a row. They are also involved in quantifying the demand. It's a critical role. ●

- 1 Seasonal Malaria Chemoprevention: previously termed intermittent preventive treatment in children, is the intermittent administration of full treatment courses of an effective antimalarial medicine during the malaria season to prevent malarial illness.
- 2 WHO Policy Recommendation: Seasonal Malaria Chemoprevention (SMC) for *Plasmodium falciparum* malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. Geneva: World Health Organization Global Malaria Programme; March 2012: http://www.who.int/malaria/publications/atoz/smc_policy_recommendation_en_032012.pdf
- 3 WHO/GMP Technical Expert Group On Preventive Chemotherapy, Geneva 4-6 May 2011. Report of the technical consultation on seasonal malaria chemoprevention: http://www.who.int/malaria/mpac/feb2012/smc_teg_report.pdf
- 4 Lubell Y et al. "Cost-effectiveness of parenteral artesunate for treating children with severe malaria in sub-Saharan Africa." *Bull World Health Organ.* 89(7):504-12 (2011).
- 5 UNITAID-funded ACCESS-SMC consortium includes: Malaria Consortium (prime recipient), Catholic Relief Services (joint lead), MMV, Management Sciences for Health, Speak Up Africa, London School of Hygiene and Tropical Medicine
- 6 Cairns M et al. "Estimating the potential public health impact of seasonal malaria chemoprevention in African children." *Nat Commun.* 3:881. (2012).



Medicines for Malaria Venture (MMV) receives funding and support from government agencies, private foundations, international organizations, corporate foundations and private individuals (Figure 1). These funds are used to finance MMV's portfolio of research and development (R&D) projects to develop new, effective and affordable medicines for the treatment and prevention of malaria. They also support specific, targeted access and product management (APM) interventions to help ensure that vulnerable populations in malaria-endemic countries can access new malaria medicines.

As a not-for-profit Swiss foundation set up under statutes dated 15 November 1999, MMV is exempt from cantonal and federal taxes and is the equivalent of an exempt organization within the meaning of Section 501(c) (3) of the United States Internal Revenue Code. Furthermore, from 1 January 2011, the Swiss Federal Council granted MMV the status of 'Other International Organization' conferring certain privileges and immunities including exemption from VAT in

Switzerland – representing an estimated additional contribution from Switzerland to MMV of up to Swiss Francs (CHF) one million per annum.

Portfolio funding

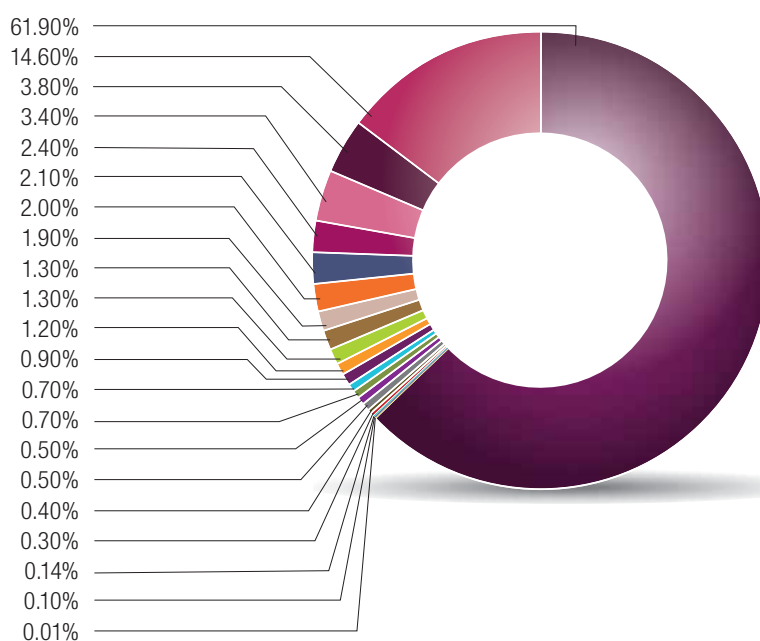
The prolonged effects of the global economic downturn continued to have an impact on financial operations throughout 2014. Prudent financial management involved careful negotiation of contractual agreements and increased in-kind contributions from partners. We estimate that for every USD 1 invested, MMV leverages approximately USD 3.5 of R&D value (i.e. USD 1 in matched funds for external costs plus USD 1.50 in in-kind contributions, such as staff and facilities). In 2014, our two largest donors, the Bill & Melinda Gates Foundation and the UK Department for International Development (DFID), extended programmatic supplements to their already significant long-term commitments, which were renewed in 2013. Moreover, thanks to dynamic financial management coupled with proactive fundraising, MMV's R&D portfolio and APM

activities for the year were realized. MMV's drug R&D activity and corresponding expenditure in 2014 (USD 49.5 million) was in line with 2013 (USD 50.2 million). Overall, MMV's expenditure of USD 67.2 million increased by 3% compared with USD 65.2 million in 2013 mainly owing to an increase in APM expenditure from USD 6.1 million in 2013 to USD 8.7 million in 2014.

Since its foundation in 1999, MMV has spent USD 628 million to build the world's largest R&D portfolio of new and innovative antimalarial medicines: five of which have been launched and are being used to treat patients in malaria-endemic countries. Our business plan estimates needing a minimum of USD 292 million over the period 2015–2018 in order to sustain this work. With approximately USD 115 million available, (outstanding committed pledges as at the end of 2014 as well as cash brought forward to 2015), the organization is currently tracking a shortfall from 2017 onwards. MMV has several pending proposals to donors and remains active in its resource mobilization and advocacy activities.

Figure 1. Total funding received/pledged from 1999 to 2018 – USD 865.3 million at 31 December 2014

Bill & Melinda Gates Foundation
UK Department for International Development (DFID)
UNITAID
Wellcome Trust
United States Agency for International Development (USAID)
Irish Aid
Netherlands Minister for Development Cooperation
Swiss Government SDC
National Institutes of Health (NIH)
Spanish Agency for International Development
Australian Government Department of Foreign Affairs and Trade (DFAT)
World Bank
Rockefeller Foundation
ExxonMobil Foundation
Newcrest Mining Limited
Global Health Innovative Technology Fund (GHIT)
World Health Organization/Roll Back Malaria (WHO/RBM)
Norwegian Agency for Development Cooperation (NORAD)
Individual and other donors
BHP Billiton
EU CRIMALDDI





Financial year to 31 December 2014

Details

MMV income

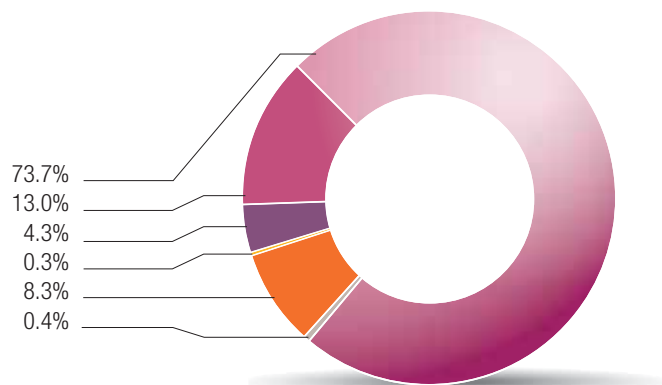
2014	USD	79,221,703
2013	USD	62,662,422
2012	USD	57,984,195
2011	USD	67,285,068
2010	USD	58,122,675
2009	USD	42,180,117
2008	USD	55,148,885
2007	USD	76,965,380
2006	USD	30,618,703
2005	USD	44,770,355
2004	USD	28,705,652
2003	USD	21,712,944
2002	USD	10,586,792
2001	USD	13,599,677
2000	USD	7,606,949

Research & development expenditure

2014	USD	49,537,276
2013	USD	50,165,812
2012	USD	60,756,529
2011	USD	40,330,004
2010	USD	42,544,044
2009	USD	44,298,951
2008	USD	46,028,889
2007	USD	41,494,679
2006	USD	46,943,252
2005	USD	27,166,334
2004	USD	23,805,411
2003	USD	16,950,454
2002	USD	10,353,468
2001	USD	6,709,653
2000	USD	2,280,748

Figure 2. MMV expenditure 2014
Total: USD 67.2 million

R&D	73.7%
Access & Product Management	13.0%
External Relations & Advocacy	4.3%
Foundation Board & Stakeholders	0.3%
General & Administration	8.3%
Others	0.4%



Management and auditing

Auditing of MMV's accounts is conducted annually by KPMG. Relationships with two major Swiss banks allow us to effectively manage our global banking relationships and diversify risk. The banks provide services such as current accounts, investment and cash management facilities in multiple currencies.

Financial reporting standards

The 2014 financial statements were prepared in compliance with Swiss GAAP FER. MMV had previously followed International Financial Reporting Standards (IFRS). The transition to Swiss GAAP FER did not alter the transparency and disclosure in any significant way. The organization's operating procedures are constantly updated in line with evolving requirements.

Foundation capital

By 31 December 2003, the stipulated foundation capital of USD 4 million was fully subscribed (in a Swiss foundation it is a legal requirement that the foundation capital should be constituted without delay in order to provide a degree of financial security for the foundation). The foundation capital remained unchanged at 31 December 2014.

Donations and pledges 2014

(see Note 6, page 41, Donations)

Cash donations received in the bank amounted to a total of USD 77,285,432 with income recognized in the previous year (2013) of USD 460,963, income deferred from the previous year (2013) of USD 3,870,917 and income deferred to the following year (2015) of USD 5,759,025. Current 2014 income, to be received in early 2015 amounted to USD 2,081,748. Income of USD 14,200 was recognized from MMV North America Inc.

General & administration expenditure

General and administration cost increases were kept consistently low during 2014. MMV's staff headcount increased to 55 from 54 in 2013. The ratio of general and administration expenditure to overall spending decreased to 8.3% from 9.3% in 2013 (8.5% from 9.5% in 2013 if board and stakeholders expenses are included). This compared with 7.8% in 2012, 9.6% in 2011, 10.7% in 2010, 9.15% in 2009, 10.6% in 2008, 9.7% in 2007, 6.8% in 2006 and 11.1% in 2005.

New pledges received in 2014

DONOR	Amount (in millions)	Period
Bill & Melinda Gates Foundation – Innovation fund	USD 1.6	2014–2015
Bill & Melinda Gates Foundation – OZ439/TQ acceleration supplement	USD 24.3	2014–2017
Bill & Melinda Gates Foundation – QIMR supplement	USD 9.2	2014–2018
UK Department for International Development (DFID) supplement	£3.0 (USD 4.8)	2014–2015
Japanese GHIT Fund	JPY 129 (USD 1.2)	2014–2015
UNITAID*	USD 2.0	2014–2017
Total (USD equivalent)	43.1	

*MMV is a sub-recipient via the prime recipient, the Malaria Consortium.

Fundraising

In addition to previous pledges, MMV received several new pledges in 2014 as fundraising continued to progress (see table above). MMV is grateful for these and previous commitments from its many donors.

Financial year ahead to December 2015

MMV operates in a complex multi-currency environment. The accounts are kept in US Dollars. The bulk of donations are received in US Dollars and UK Pounds Sterling, although other currencies are sometimes involved. Outflows for projects are also mostly in USD, which is the standard currency used in the various specific contractual agreements signed with each project partner and therefore a natural cover for financial exchange risk. On the other hand, many operational expenses are in Swiss Francs (CHF). The resulting exposure or exchange risk is hedged, according to the budget in January, to provide a nominal fixed average USD/CHF budget rate for the period.

The philosophy underlying MMV's financial management is that of prudent, conservative

control, including appropriate return on interim treasury investments. Forecasting various long-term funding and income scenarios enables MMV to manage its growing R&D portfolio more effectively. It also provides a baseline analysis for fundraising activities aimed at financing the portfolio in line with long-term projections.

Given the unsteady financial environment and market conditions, it is evident that the portfolio, cash flow and new potential fundraising opportunities have to be managed dynamically and seamlessly.

Focus on sustainability: R&D and APM

In 2014, MMV continued to prepare, scale-up and launch activities to ensure market access to medicines emerging from its pipeline. These activities enable a 'downstream' extension of the public-private partnership model underpinning MMV's overarching goal to achieve major health impact from its medicines. Moreover, in the context of malaria elimination and eradication, a second and critical series of investments are now urgently needed to spur

on R&D for the next-generation of antimalarial drugs to meet that goal.

Although fundraising remains successful and significant additional funds were sourced in 2014, major fundraising efforts will be required in 2015 and even more in 2016 and beyond, as MMV strives to meet the projected financial requirements of its growing portfolio.

Financial modelling

Financial modelling suggests that, in spite of additional future funding pledges for MMV in 2015 and pending proposals to donors, future R&D and APM activities will remain underfunded.

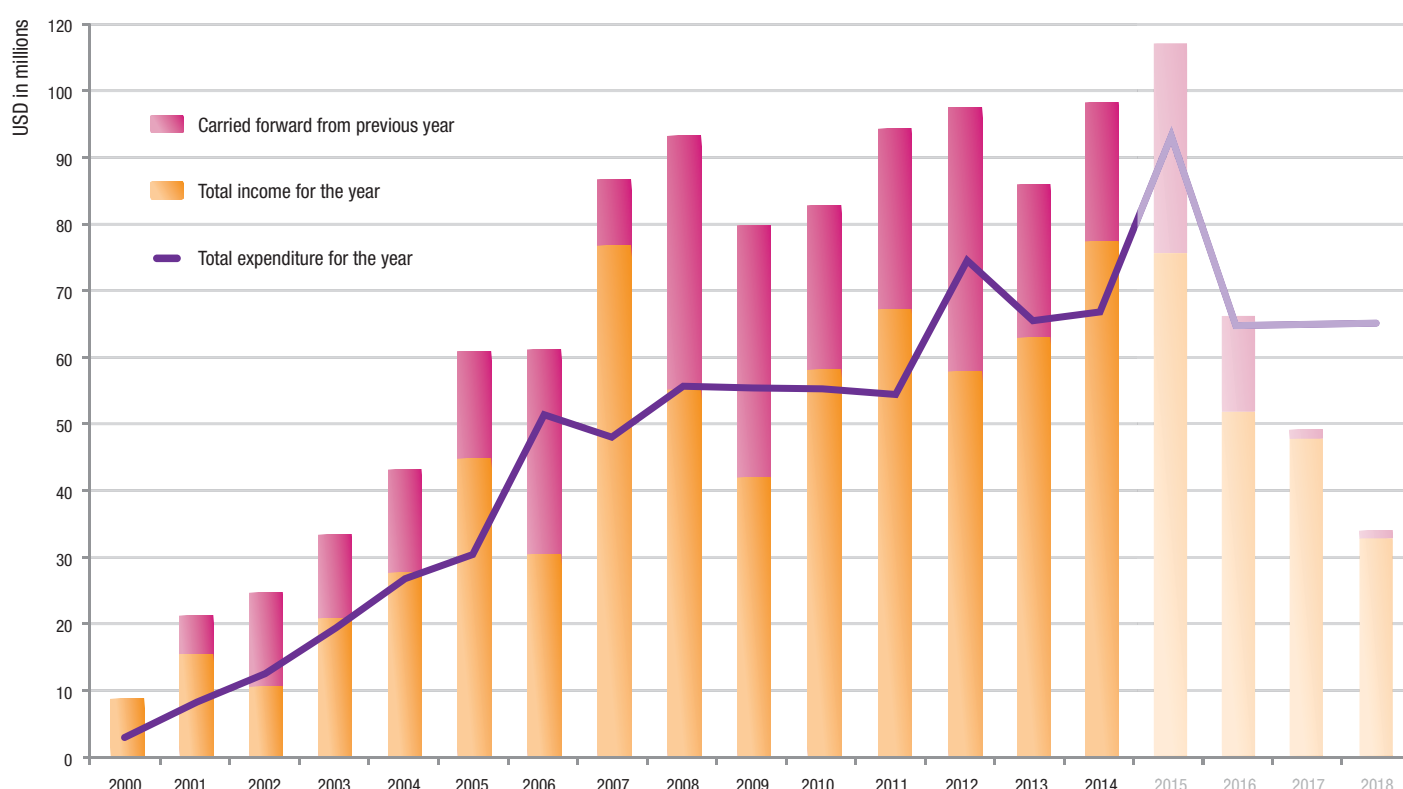
The long-term financial projections for future MMV overall spending over 2015–2018 is USD 292 million. This figure represents a mixture of R&D, product launch and APM-related spending, including much needed innovation in treatments for malaria in pregnancy, *Plasmodium vivax* malaria, transmission blocking and other technologies for elimination and eradication.

These financial statements and all forward-looking financial figures should be considered as management's best estimates based on information available at the time of printing (June 2015).

Financial tables

The financial tables and notes that follow are extracted from the Swiss GAAP FER compliant accounts.

Figure 3. MMV income and expenditure to date and scenario 2015–2018



MMV CONSOLIDATED STATEMENT OF FINANCIAL POSITION

			31 Dec 2014 USD	31 Dec 2013 USD
ASSETS		Notes		
CURRENT ASSETS				
	Cash And Cash Equivalents	3	38 057 339	32 954 528
	Donations Receivable	6	2 081 748	452 567
	Project Reimbursements Receivable		–	5 710
	Accounts Receivable		2 503 016	26 225
	Tax Receivable		6 002	5 302
	Prepays		447 087	347 425
	Prepaid R&D Commitments	7	3 175 421	275 831
	Prepaid APM Commitments	7	3 234 746	2 063 686
TOTAL CURRENT ASSETS			49 505 359	36 131 274
LONG-TERM ASSETS				
	Guarantees	15	191 523	191 361
	Fixed Assets, Net	4	313 595	229 686
TOTAL LONG-TERM ASSETS			505 118	421 047
TOTAL ASSETS			50 010 477	36 552 321
LIABILITIES AND CAPITAL & RESERVES				
CURRENT LIABILITIES				
	Accrued R&D Commitments	7	6 823 803	6 765 293
	Accrued APM Commitments	7	2 347 264	548 034
	Deferred Income	6	5 759 025	4 127 882
	Other Creditors		875 267	771 267
	Accrued Expenses		1 724 238	2 888 107
	Short-Term Provisions	5	450 056	439 291
	Donations Reimbursement Payables	9	320 653	–
TOTAL CURRENT LIABILITIES			18 300 306	15 539 874
RESTRICTED FUNDS				
	Restricted Operating Funds		10 435 263	7 525 410
TOTAL RESTRICTED FUNDS			10 435 263	7 525 410
CAPITAL & RESERVES				
	Foundation Capital		4 000 000	4 000 000
	Unrestricted Operating Funds		17 274 908	9 487 037
TOTAL CAPITAL & RESERVES			21 274 908	13 487 037
TOTAL LIABILITIES AND CAPITAL & RESERVES			50 010 477	36 552 321

MMV CONSOLIDATED STATEMENT OF COMPREHENSIVE INCOME

Continuing Operations		31 Dec 2014	31 Dec 2013
INCOME	Notes	USD	USD
DONATION REVENUES			
Private Foundations & Individual Donors		43 215 524	36 806 795
UN Agencies		7 288 713	3 420 000
Government Agencies		25 152 286	21 419 227
Corporates & Corporate Foundations		1 367 836	761 305
<i>Total Restricted Donations</i>		<i>24 516 099</i>	<i>21 135 760</i>
<i>Total Unrestricted Donations</i>		<i>52 508 260</i>	<i>41 271 567</i>
TOTAL DONATION REVENUES	6	77 024 359	62 407 327
OTHER INCOME	9	2 197 344	215 095
TOTAL INCOME		79 221 703	62 622 422
EXPENDITURE			
RESEARCH & DEVELOPMENT EXPENDITURE			
Project Grants	7	37 609 518	36 818 961
Project-Related Variable Expenditure	7	11 533 558	12 833 182
Expert Scientific Advisory Council Expenses		394 200	513 669
TOTAL RESEARCH & DEVELOPMENT EXPENDITURE		49 537 276	50 165 812
ACCESS & PRODUCT MANAGEMENT EXPENDITURE			
Project Expenditure	7	6 803 784	4 021 164
Access-Related Variable Expenditure		1 824 705	2 002 626
Access & Product Management Advisory Committee		104 494	95 836
TOTAL ACCESS & PRODUCT MANAGEMENT EXPENDITURE		8 732 983	6 119 626
EXTERNAL RELATIONS & ADVOCACY EXPENDITURE			
ER&A-Related Variable Expenditure		2 652 442	2 444 371
Fundraising		43 619	49 437
Communications		173 515	206 745
TOTAL EXTERNAL RELATIONS & ADVOCACY EXPENDITURE		2 869 576	2 700 553
FOUNDATION BOARD & STAKEHOLDER EXPENDITURE	13	172 950	158 789
GENERAL & ADMINISTRATION EXPENDITURE			
Staff-related Benefits/Compensation	8	3 439 573	3 888 772
Office and Occupancy	11	1 238 742	1 270 448
Travel Expenses		58 044	39 965
Professional and Legal Fees		77 859	111 533
Training, Education and Journals		23 940	37 332
IT expenses		497 180	323 932
Depreciation	4	105 574	94 818
Other		172 083	293 263
TOTAL GENERAL & ADMINISTRATION EXPENDITURE		5 612 995	6 060 063
OTHER EXPENSES		320 653	27 947
TOTAL EXPENDITURE		67 246 433	65 232 790
RESULT FROM OPERATING ACTIVITIES		11 975 270	(2 610 368)
Interest Income		101 405	157 656
Financial Expenses		(41 588)	(37 099)
Foreign Currency Translation Differences	10	(1 337 363)	175 559
Net Financial Result		(1 277 546)	296 116
(LOSS)/SURPLUS FOR THE PERIOD		10 697 724	(2 314 252)
ALLOCATIONS			
Transfer (To)/From Operations Reserve		(7 395 853)	8 192 852
Transfer (To)/From Donor Restricted Reserve		(3 301 871)	(5 878 600)
		(10 697 724)	2 314 252

MMV CONSOLIDATED STATEMENT OF CASH FLOW

	Notes	2014 USD	2013 USD
(LOSS)/SURPLUS FOR THE YEAR		(10 697 724)	(2 314 252)
Adjustments for:			
Increase/(Decrease) in Provisions	5	10 765	26 050
Depreciation	4	105 574	94 818
OPERATING RESULT BEFORE WORKING CAPITAL CHANGES		(10 814 063)	(2 193 383)
CASH FLOW FROM OPERATING ACTIVITY			
(Increase) in Donations Receivable		(1 631 759)	(77 148)
Decrease/(Increase) in Project Balance Reimbursements		5 710	(4 185)
(Increase)/Decrease in Accounts Receivable		(2 476 888)	24 248
(Increase)/Decrease in Tax Receivable		(700)	33 607
(Increase) in Project-Related Prepaid Expenses	7	(4 070 650)	(122 815)
(Increase)/Decrease in Prepaid Expenses		(103 116)	262 571
Increase in Accrued R&D Commitments	7	58 510	2 540 633
Increase in Accrued APM Commitments	7	1 800 580	295 098
Increase in Deferred Income	6	1 631 143	2 591 766
Increase in Other Creditors		103 922	227 620
(Decrease)/Increase in Accrued Expenses		(1 165 220)	1 006 372
Increase in Donations Reimbursement Payables		320 653	–
Unrealized Foreign Currency (Gain)/Loss		382 066	243 240
CASH FLOW RESULTING FROM OPERATING ACTIVITY		(5 145 749)	7 021 009
CASH FLOW FROM INVESTMENT ACTIVITY			
Increase in Guarantees		(5 201)	(11 700)
(Increase) in Fixed Assets	4	(189 483)	(13 075)
CASH FLOW RESULTING FROM INVESTMENT ACTIVITY		(194 684)	(24 774)
NET (DECREASE)/INCREASE OF CASH AND CASH EQUIVALENTS		5 473 630	4 802 851
Cash & Cash Equivalents at Beginning of Year		32 954 528	28 412 564
Effect of Exchange Rate Fluctuations on Cash Held		(370 819)	(260 887)
Cash & Cash Equivalents at End of Year		38 057 339	32 954 528

MMV CONSOLIDATED STATEMENT OF CHANGES IN EQUITY

	Balance at 1 Jan 2013	Gain/(Loss) for the Period	Balance at 31 Dec 2013	Internal Funds Transfer	Gain for the Period	Balance at 31 Dec 2014
Restricted Operating Funds	1 646 810	5 878 600	7 525 410	(392 018)	3 301 871	10 435 263
TOTAL RESTRICTED OPERATING FUNDS	1 646 810	5 878 600	7 525 410	(392 018)	3 301 871	10 435 263
Foundation Capital	4 000 000		4 000 000			4 000 000
Unrestricted Operation Funds	17 679 889	(8 192 852)	9 487 037	392 018	7 395 853	17 274 908
TOTAL UNRESTRICTED FUNDS	21 679 889	(8 192 852)	13 487 037	392 018	7 395 853	21 274 908

NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS AT 31 DECEMBER 2014

1. ORGANIZATION

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

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

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

2. SIGNIFICANT ACCOUNTING POLICIES

The significant accounting policies adopted by MMV in the preparation of the consolidated financial statements are set out below.

Statement of compliance

The consolidated financial statements for the year ending 31 December 2014 were approved for issue by the MMV Board on 12 March 2015.

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

As donations from governments are not being addressed in the Swiss GAAP FER 21, the organization has decided to retain the accounting treatment prescribed by IAS 20, namely recognize income up to the amount of expenditure allocated by government, the difference being recognized as deferred income.

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

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

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

Basis of preparation

The consolidated financial statements are presented in US Dollars, since the majority of MMV's activities are conducted in this currency (group functional and presentation currency).

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

Judgements made by management in the application of Swiss GAAP FER that have significant effect on the consolidated financial statements and estimates with a significant risk of material adjustment in the next year are discussed below.

Foreign currency transactions

Transactions in foreign currencies are translated at the foreign exchange rate ruling at the date of the transaction. Monetary assets and liabilities denominated in foreign currencies at the Consolidated Statement of Financial Position date are translated to USD at the foreign exchange rate ruling at that date. Foreign exchange differences arising on translation are recognized in the Consolidated Statement of Comprehensive Income. Non-monetary assets and liabilities that are measured in terms of historical cost in a foreign currency are translated using the exchange rate at the date of the transaction.

The following exchange rates were used at year end:

2014

→ 1 CHF	=	USD	1.0105
→ 1 EUR	=	USD	1.2155
→ 1 GBP	=	USD	1.5532
→ 1 AUD	=	USD	0.8156

2013

→ 1 CHF	=	USD	1.1244
→ 1 EUR	=	USD	1.3780
→ 1 GBP	=	USD	1.6562
→ 1 AUD	=	USD	0.8947

Cash and cash equivalents

Cash and cash equivalents comprise cash balances and short-term money market deposits with original maturities of three months or less.

Fixed or tangible assets

Fixed assets are stated at cost less accumulated depreciation. Depreciation is charged to the Consolidated Statement of Comprehensive Income on a straight line basis over the estimated useful lives of the assets. The estimated useful lives of assets are as follows:

→ Office furniture	5 years > CHF 1,000
→ Fixtures and installations	3 years > CHF 1,000
→ Computers and equipment	3 years > CHF 5,000

Impairment

The carrying amounts of MMV's assets are reviewed at each Consolidated Statement of Financial Position date to determine whether there is an indication of impairment. If any such indication exists, the asset's recoverable amount is estimated. An impairment loss is recognized in the Consolidated Statement of Comprehensive Income whenever the carrying amount of an asset exceeds its recoverable amount.

The recoverable amount of an asset is the greater of its value in use and its fair value less costs to sell. In assessing value in use, the estimated future cash flows are discounted to their present value using a pre-tax discount rate that reflects current market assessments of time, value of money and the risks specific to the asset.

Provisions

A provision is recognized in the Consolidated Statement of Financial Position 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.

Foundation capital

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

Revenue recognition

An unconditional grant is recognized as revenue in the Consolidated Statement of Comprehensive Income when the grant becomes receivable. Any other grant which has performance, timing or other conditions is recognized in the Consolidated Statement of Financial Position 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 12. They are considered as unrestricted funds, unless the donor stipulates a specific restriction.

A reconciliation between donations received in cash and income recognized in the Consolidated Statement of Comprehensive Income is shown in note 6.

Government grants are recognized as income for the allowable expenses incurred in the current year. At year end, the difference between the income recognized and the cumulative expenses incurred is accounted for as deferred income.

When the donor wishes to see a donation allocated to a specific cause, the donation is considered to be an allocated fund. Allocated funds that have not been used at the end of the year are presented in a separate section of the Statement of Financial Position.

Contributions in kind

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

Operations reserve

The accumulated operations reserve represents excess of core grants over expenditure since the inception of MMV and is available to be utilized for future operation and project funding costs as the rapidly evolving research and development project pipeline dictates.

Interest income and financial expense

Interest income and financial expense comprise interest on funds invested and bank charges.

Research and development expenditure

Expenditure and grants allocated for research and development activities undertaken with the prospect of gaining new scientific or technical knowledge and understanding are recorded on the basis of contracts with grantees. In the event that a portion of a grant is unpaid at the year end, it is

included under current liabilities. Expenses paid before year end for the following period are recorded as Prepaid R&D Commitments in current assets and as Prepaid in Note 7.

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

Income tax and status

MMV received exoneration from income tax from the Geneva cantonal and Swiss federal authorities from the year 2000 for an indeterminate period.

A further agreement was signed on 8 December 2010 with the Swiss Federal Council under new provisions of the recently promulgated Swiss Host State Act, to grant MMV certain privileges and immunities – effective from 1 January 2011.

The principal advantages for MMV as a Swiss foundation with 'Other International Organization' status are the following:

- Exoneration from all direct and indirect federal, cantonal and communal taxes (this was originally acquired by decree with the Geneva cantonal and Swiss federal authorities, but now formalized directly with the Swiss government within the accord).
- Exoneration from VAT on all goods and services acquired for the sole use of the foundation within Switzerland and abroad.
- Unrestricted access to work permits for non-Swiss and non-EU nationals.

MMV will deal directly with the Swiss Mission in Geneva for all such issues.

Basis of consolidation

MMV has established a Special Purpose Entity (SPE) for fundraising in North America (MMV, North America, Inc.). MMV does not have any direct or indirect shareholdings in this entity.

An SPE is consolidated if, based on an evaluation of the substance of its relationship with MMV and the SPE's risks and rewards, MMV concludes it controls the SPE. The SPE is not fully controlled by MMV, but was established under such terms and conditions that it imposes strict limitations on the decision-making powers of the SPE's management with the result that MMV receives the majority of the benefits related to the SPE's operations and net assets while being exposed to the majority of risks incident to the SPE's activities, and retaining the majority of the residual or ownership risks related to the SPE or its assets. MMV appoints the board members of the SPE.

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

List of organizations consolidated in 2014:

Country	United States of America
Name and domicile	MMV, North America, Inc. Delaware
Functional currency	USD
% controlled by MMV	N/A*
Direct/Indirect	N/A

*Not applicable.

Transactions eliminated on consolidation

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

Accounting estimates and judgements

Certain critical accounting judgements in applying MMV accounting policies are described below.

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

Research and Development Expenditure – MMV's R&D expenditure is generally not direct expenditure, but is in the form of grants and contracts with external parties who perform certain tasks at MMV's 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 from the original plans. These factors lead to subjectivity in the timing and recognition of research and development expenditure.

3. CASH AND CASH EQUIVALENTS

	31 December 2014 USD	31 December 2013 USD
Cash	1 513	6 632
Bank Balances	34 055 826	30 947 896
Money Market Deposits	4 000 000	2 000 000
TOTAL CASH AND CASH EQUIVALENTS	38 057 339	32 954 528

The effective rates on deposits have moved within the following ranges:

	2014		2013	
	Low %	High %	Low %	High %
US Dollar (USD)	0.00	0.60	0.00	0.20
Swiss Franc (CHF)	0.01	0.025	0.03	0.05
British Pound (GBP)	0.00	0.00	0.00	0.00
Euro (EUR)	0.01	0.05	0.05	0.05
Australian Dollar (AUD)	0.00	0.00	0.00	0.00

4. FIXED ASSETS

2014	Fixtures & Installations USD	Office Furniture USD	Computers & Equipment USD	Total USD
COST				
At 1 January 2014	492 511	395 462	527 241	1 415 214
Additions	60 302	44 260	84 921	189 483
Disposals	–	(503)	(13 111)	(13 614)
AT 31 DECEMBER 2014	552 813	439 219	599 051	1 591 082
ACCUMULATED DEPRECIATION				
At 1 January 2014	362 709	343 426	479 393	1 185 528
Charge for the Year	38 040	18 731	48 802	105 574
Disposals	–	(503)	(13 110)	(13 614)
AT 31 DECEMBER 2014	400 749	361 654	515 085	1 277 488
NET BOOK VALUE				
AT 31 DECEMBER 2014	152 064	77 565	83 966	313 595

The fire insurance value of the tangible fixed assets is USD 1,717,850 (2013: USD 1,822,000).

5. PROVISIONS

	Unused Vacation Reserve USD	Bad Debt Provision USD	Total Provisions USD
BALANCE AT 1 JANUARY 2013	398 362	14 879	413 241
Use/Release 2013	(398 362)	(14 879)	(413 241)
Allocation for the Year	439 291	–	439 291
BALANCE AT 31 DECEMBER 2013	439 291	–	439 291
Use/Release 2014	(439 291)	–	(439 291)
Allocation for the Year	450 056	–	450 056
BALANCE AT 31 DECEMBER 2014	450 056	–	450 056

6. DONATIONS

Below is a summary of donations received or committed during 2014:

	Cash Received 2014	Income Recognized during Previous Year	Income Deferred from Previous Year	Income Deferred to Following Year	Current Year Income to be Received	Unrealized Foreign Exchange Gain/(Loss)	Total Income as per Statement of Comprehen- sive Income USD
	USD	USD	USD	USD	USD	USD	USD
Bill & Melinda Gates Foundation	37 531 513	–	–	–	–	–	37 531 513
Bill & Melinda Gates Foundation (Innovation Fund)	810 000	–	–	–	–	–	810 000
Bill & Melinda Gates Foundation (QIMR)	1 743 144	–	–	–	–	–	1 743 144
Wellcome Trust	1 600 000	–	–	–	–	–	1 600 000
GHIT	1 361 850	–	–	–	–	–	1 361 850
Swiss Government (DEZA/SDC)	1 785 600	–	–	–	–	–	1 785 600
UK Government (DFID)	23 388 206	–	1 118 420	(5 759 025)	–	–	18 747 601
US Government (USAID)	10 968	–	–	–	–	–	10 968
Irish Aid	–	–	1 380 600	–	–	–	1 380 600
Australian Government (DFAT)	–	–	1 371 897	–	–	–	1 371 897
Norwegian Government (NORAD)	785 749	–	–	–	–	–	785 749
National Institutes of Health (NIH)	920 221	(194 193)	–	–	343 844	–	1 069 871
UNITAID	6 047 156	–	–	–	1 241 557	–	7 288 713
ExxonMobil	500 000	–	–	–	–	–	500 000
Newcrest Mining Limited	402 611	(218 535)	–	–	236 619	–	420 694
Malaria Consortium (SMC)	–	–	–	–	157 817	–	157 817
Merck KGaA	373 215	(34 235)	–	–	98 911	6 251	444 142
Individual Donors	25 200	(14 000)	–	–	3 000	–	14 200
TOTAL RECEIVED	77 285 432	(460 963)	3 870 917	(5 759 025)	2 081 748	6 251	77 024 359

Of the total donations recognized in the Consolidated Statement of Comprehensive Income, USD 14,200 have been received through MMV, North America, Inc.

7. PROJECT GRANTS

Project Name	Awarded 2014 (USD)	Final Allocation 2014 (USD)	Paid 2014 (USD)	Related to 2014 paid in 2015 (USD)	Prepaid 2014 for 2015 (USD)	Project Partners
Hit Identification	2 734 999	1 355 093	1 619 437	(264 344)	1 379 907	
1 Pathogen Box	549 008	549 008	713 352	(164 344)	-	Evotec, TCG Lifescience Ltd
2 G-HIT Screening Program	114 910	114 910	114 910	-	-	Giffith University
3 St George's Screening	11 346	11 346	11 346	-	-	Penn Pharmaceutical Serv.
4 Challenge Grants/Library Purchase	700 000	-	100 000	(100 000)	700 000	Medicines for Malaria Venture
5 Compound Acquisition/Synthesis	130 035	43 369	43 369	-	86 667	TCG Lifesciences Ltd
6 Biofocus Library 250,000 Compounds	1 179 700	610 800	610 800	-	568 900	Biofocus
7 Challenge Grants	50 000	25 660	25 660	-	24 340	Medicines for Malaria Venture
Hit to Lead	248 552	107 973	108 905	(932)	140 579	
8 Open Source Drug Discovery in Australia	58 463	40 874	40 874	-	17 589	University of Sydney
9 Long Duration Heterocycles-Brazil Antimalarial Project	90 089	63 737	64 669	(932)	26 352	Universidade Estadual De Campinas (UNICAMP)
10 Exploring Proguanil for Delayed Death	100 000	3 362	3 362	-	96 638	Giffith University
Lead Optimization	5 022 260	5 022 260	5 532 864	(510 604)	-	
11 AstraZeneca (Miniportfolio 5)	160 314	160 314	160 314	-	-	Syngene
12 GSK (Miniportfolio 1)	2 160 000	2 160 000	2 160 000	-	-	GSK
13 Novartis (Miniportfolio 2)	705 340	705 340	705 340	-	-	Novartis Institute for Tropical Diseases
14 Sanofi Aventis (Miniportfolio 4)	234 526	234 526	234 526	-	-	Sanofi
15 DPI UCT H2L (Aminopyridine)	240 272	240 272	240 272	-	-	Technology Innovation Agency, University of Cape Town
16 St Jude/Rutgers/USF Antimalarials (NIH funding)	1 069 380	1 069 380	1 398 157	(328 777)	-	Rutgers University, St Jude Children's Research Hospital, University of South Florida, (NIH funding)
17 Anacor Oxaboroles	395 713	395 713	520 825	(125 112)	-	Anacor
18 Broad/Genzyme (miniportfolio)	56 715	56 715	113 430	(56 715)	-	Genzyme
Discovery Platform Technologies (Elimination)	4 199 949	4 098 347	4 552 413	(454 066)	101 602	
Cross Functional	2 813 936	2 765 315	2 978 761	(213 446)	48 621	
19 Outsourcing Budget	155 640	155 640	172 186	(16 546)	-	Medicines for Malaria Venture
20 Compound Management	85 359	85 359	91 352	(5 993)	-	SPECS
21 GSK Translational Pharmacology Group	667 000	667 000	667 000	-	-	GSK
22 Swiss Tropical and Public Health Institute (Swiss TPH)	607 303	606 623	606 623	-	680	Swiss Tropical and Public Health Institute (Swiss TPH)
23 Monash ODCO	299 998	252 057	396 093	(144 036)	47 941	Monash University
24 CRO Chemistry	489 859	489 859	489 859	-	-	Syngene
25 Syngene Parasitology	93 300	93 300	95 574	(2 274)	-	Syngene
26 <i>P. vivax</i> in vitro Resistance Testing	25 940	25 940	25 940	-	-	Menzies, School of Health Research, Australia
27 Malaria Lab Resistance Mutants Fidock	200 000	200 000	237 398	(37 398)	-	Columbia University, New York
28 Field Isolates Resistance	43 596	43 596	43 596	-	-	Swiss TPH, Centre Suisse de Recherches Scientifiques en Côte d'Ivoire
29 Artemisinin – Resistance in vitro	92 373	92 373	99 572	(7 199)	-	Institut Pasteur du Cambodge
30 Other diseases – Screening Activities	53 568	53 568	53 568	-	-	DNDi, GATB
P. vivax hypnozoites	400 116	347 136	403 591	(56 456)	52 981	
31 In vivo Assay of Compounds with Haemolytic Liabilities	49 929	49 929	87 300	(37 371)	-	State University of New York, Upstate Medical University
32 Primaquine mechanism	103 242	50 261	50 261	-	52 981	University of Liverpool
33 Development of a Liver Stage <i>P. vivax</i> in vitro Assay	246 946	246 946	266 030	(19 085)	-	University of California San Diego, School of Medicine

			679 805	679 805	844 885	(165 080)	-
	Transmission blocking						
34	Gametocyte Assay Development and Screen (Stage Specific)		304 805	304 805	397 795	(92 991)	- Imperial College London
35	Drug Assay Platform for Inhibition of <i>P. falciparum</i> Transmission Stages		70 000	70 000		-	TropiQ Health Science, the Netherlands
36	GSK Insectary		305 000	305 000	377 090	(72 090)	- GSK
	Chemoprotection/Prophylaxis		306 091	306 091	325 176	(19 085)	-
37	Development of a <i>P. berghei</i> uHTS Liver Stage Assay and Screening of Biofocus Library		306 091	306 091	325 176	(19 085)	- University of California San Diego, School of Medicine
	Preclinical development		2 239 745	2 239 745	3 177 990	(938 245)	-
38	ELQ-300		137 545	137 545		-	- Global Health Innovation Technology (GHIT)
39	P218		759 687	759 687	1 181 868	(422 181)	- Biotec, Thailand
40	DDD498 (Dundee University)		1 342 513	1 342 513	1 858 577	(516 064)	- Dundee University
	Phase I		4 391 249	4 371 539	5 426 251	(1 054 712)	19 710
41	MMV390048		1 715 518	1 715 518	2 016 285	(300 767)	- University of Cape Town
42	Intrarectal Artesunate (UNITAID)		475 629	475 629	504 075	(28 446)	- Cipla, Strides Arcolab
43	DSM265-DHODH Inhibitors		2 104 610	2 084 901	2 718 034	(633 134)	19 710 GHIT, Takeda
44	DSM265-OZ439 Combo		95 491	95 491	187 857	(92 366)	- Queensland Institute of Medical Research
	Proof of concept (Phase II)		-	-	-	-	-
	Translational Platform Technologies (Elimination)		1 119 956	1 119 956	1 566 003	(446 048)	-
45	Clinical Relapse Human POC		184 094	184 094	210 702	(26 608)	- Eijkman Institute, Indonesian Army
46	The Pilot Controlled Human Malaria Infection Study		816 143	816 143	1 235 583	(419 440)	- Queensland Institute of Medical Research
47	QIMR Controlled Human Malaria Infection Model Due Diligence		119 719	119 719	119 719	-	- Swiss TPH
	Phase IIB		11 163 136	11 085 168	13 756 975	(2 671 807)	77 968
48	OZ439		3 714 294	3 664 466	5 652 445	(1 987 979)	49 829 Sanofi
49	OZ439 Ferroquine Development		653 409	653 409	658 814	(5 405)	- Sanofi
50	OZ439 Pteriquine Development		5 489 028	5 460 888	5 567 869	(106 981)	28 139 Sanofi
51	Napthoquine (Arco)		327 320	327 320	327 320	-	- Ifakara Health Institute
52	OZ439 Add-on Therapy in Resistance		40 482	40 482	40 482	-	- Medicines for Malaria Venture
53	OZ439 Extended Observation Study		938 604	938 604	1 510 046	(571 442)	- Mahdol Oxford Tropical Medicine Research Unit (MORU)
	Phase III		5 345 987	4 459 127	4 459 127	-	886 861
54	Tafenoquine for <i>P. vivax</i> Relapse Prevention		4 648 009	3 761 148	3 761 148	-	886 861 GSK
55	Paediatric Tafenoquine for <i>P. vivax</i> Relapse Prevention		286 723	286 723	286 723	-	- GSK
56	CYP2D Phenotyping and Genotyping		411 255	411 255	411 255	-	- Eijkman Institute
	Phase IV		4 319 107	3 750 312	4 233 356	(483 044)	568 795
57	Coartem® Dispersible (Artemeter-Lumefantrine) Safety/Efficacy in children <5kgs		129 050	129 050	129 050	-	- Novartis Pharma AG
58	Coarsucam™ (Artesunate-amodiaquine) Implementation study		86 772	86 772	86 772	-	- Sanofi
59	Eurartesim® (Dihydroartemisinin-Piperaquine) New Paediatric Formulation		-	-	-	-	- Sigma-Tau Industrie Farmaceutiche Riunite, Italy
60	Pyramax® (Pyronaridine-Artesunate)		300 054	300 054	315 372	(15 318)	- Shin Poong Pharmaceutical Co Ltd
61	Pyramax® (Pyronaridine-Artesunate) New Paediatric Formulation		490 995	471 760	571 767	(100 007)	19 235 Shin Poong Pharmaceutical Co Ltd
62	Safety/Efficacy of Retreatment with ACTs (WANECAM study)		2 850 673	2 665 762	2 668 831	(3 069)	184 910 University of Bamako
63	AZ-CQ		96 914	96 914	96 914	-	- UMC St Radboud, Netherlands
64	Extended Ethiopia Malaria Trial Capacity Building		364 650	-	364 650	(364 650)	364 650 University of Vienna
	TOTAL R&D		40 784 939	37 609 518	44 433 321	(6 823 803)	3 175 421

7. PROJECT GRANTS (CONTINUED)

	Awarded 2014 (USD)	Final allocation 2014 (USD)	Paid 2014 (USD)	Related to 2014 paid in 2015 (USD)	Prepaid 2014 for 2015 (USD)	Project Partners
Introduction of New Product/Oversee Launched Product	7 945 784	5 199 030	3 400 065	1 798 965	2 746 754	
1 Policy Revision	40 182	40 182	40 182	–	–	Medicines for Malaria Venture
2 Eurartesim®	148 577	148 577	110 245	38 333	–	Imperial College London, Sigma-Tau Industrie Farmaceutiche Riunite, Italy
3 Pyramax®	6 069	6 069	6 069	–	–	Shin Poong Pharmaceutical Co. Ltd., Medicines for Malaria Venture
4 Injectable Artesunate – General	22 940	22 940	10 051	12 889	–	Medicines for Malaria Venture
5 Injectable Artesunate – Public Sector	63 729	63 729	63 729	–	–	Clinton Health Access Initiative, Swiss TPH
6 Malaria in Pregnancy IPTp	498 692	198 692	(296 271)	494 963	300 000	London School of Hygiene & Tropical Medicine
7 OZ439	30 558	30 558	30 513	45	–	
8 Seasonal Malaria Chemoprevention	122 020	122 020	114 271	7 749	–	West Africa Roll Back Malaria Network (WARN)
10 Improving Severe Malaria Outcomes	7 013 017	4 566 263	3 321 277	1 244 986	2 446 754	Clinton Health Access Initiative, Malaria Consortium, MissionPharma
Input to R&D	656 238	553 340	544 897	8 443	102 898	
11 Vivax – Market Research to Support Tafenoquine	49 996	49 996	49 915	81	–	GSK
12 Vivax – Strategy Development	410 925	334 904	334 904	–	76 021	World Health Organization
13 India Comprehensive Case Managemt Pilot	195 317	168 440	160 078	8 362	26 877	National Institute of Malaria Research India, NVBDCP Odisha
Gather & Generate Information	582 438	582 438	436 204	146 234	–	
14 Market Intelligence – General	310 905	310 905	251 410	59 495	–	Imperial College London, BroadReach Healthcare, Medicines for Malaria Venture
Market Intelligence – Analytics & Reports	369	369	369	–	–	
15 Market Volumes (Market Size & Segmentation)	271 164	271 164	184 425	86 739	–	Government of Zambia, IMS Health
New Projects/Pilots	695 332	310 237	(79 364)	389 601	385 095	
16 Interactive Map Tool – WHO GMP	2 795	2 795	2 795	–	–	Medicines for Malaria Venture
17 Oil Search	7 367	7 367	7 101	265	–	Oil Search Health Foundation
18 Newcrest Alliance	106 576	106 576	102 335	4 241	–	Newcrest Mining Limited
19 SMS for Life – Tanzania	193 500	193 500	193 500	–	–	Government of Tanzania
20 MDA Programming (Lihir)	385 095	–	(385 095)	385 095	385 095	Newcrest Mining Limited, ISGlobal – Barcelona Institute For Global Health
Access Events & Misc. Project Costs	158 738	158 738	154 718	4 020	–	
21 Events & Conferences	30 152	30 152	30 120	32	–	Medicines for Malaria Venture
22 Miscellaneous	128 586	128 586	124 598	3 988	–	PNG Industry Malaria Initiative (PIMI), World Health Organization
TOTAL	10 038 530	6 803 784	4 456 520	2 347 264	3 234 746	

Project grants represent the awards to the projects as specified above, directly managed and supervised by MMV.

Project-related variable expenditures include all legal advice/services for contract negotiations (IPR), organization and travel for project meetings/reviews, MMV scientific personnel compensation and various scientific project consultancies. Expenditure for this MMV support totalled USD 11,533,558 in 2014 and USD 12,894,036 in 2013, respectively.

Project reimbursements receivable

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

8. PERSONNEL EXPENSES

There were 55 employees at 31 December 2014, excluding temporary staff members (2013: 54).

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.

Pension plan statistics

	2014 USD	2013 USD
Capital Ratio (%)	107.4	104.7
Economic Part of the Entity at 1 January 2013	–	–
Economic Part of the Entity at 31 December 2013	–	–
Occupational Benefits Included in Personnel Expenditures	1 703 149	1 902 906
Pension Fund Liability	(320)	2 821

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 contributions from MMV and the employees.

9. OTHER INCOME AND OTHER EXPENSES

OTHER INCOME	2014 USD	2013 USD
Project Reimbursements from Previous Years	2 100 000	315
Royalties	25 000	15 000
Tax at Source Commission	28 855	26 760
Other	43 488	173 021
OTHER INCOME	2 197 343	215 096

OTHER EXPENSES	2014 USD	2013 USD
Allocation to Bad Debt	–	(27 947)
Donation Reimbursement	(320 653)	–
OTHER EXPENSES	(320 653)	(27 947)

In the course of 2014 MMV reimbursed an amount of USD 320,653 to a donor, namely Global Health Innovative Technology (GHIT) Fund, owing to the termination of clinical trials related to a specific earmarked project (ELQ300) funded by GHIT. This amount represented the unused part of a grant received in 2013.

10. FOREIGN CURRENCY TRANSLATION DIFFERENCES FOR FOREIGN OPERATIONS

FOREIGN EXCHANGE GAIN/(LOSS)	2014 USD	2013 USD
Exchange (Loss)/Gain from CHF	(769 580)	51 363
Exchange (Loss)/Gain from EUR	(93 629)	9 466
Exchange (Loss)/Gain from GBP	(479 089)	237 992
Exchange Gain from UGX	–	3
Exchange Gain/(Loss) from AUD	4 935	(123 265)
FOREIGN EXCHANGE (LOSS)/GAIN	(1 337 363)	175 559

In order to minimize the potential adverse effect of foreign exchange fluctuations, MMV's liquidity is deposited in bank accounts denominated in foreign currencies pro rata to the breakdown of total expenditure by currency (natural hedging). In the second half of 2014 most currencies (and in particular the Swiss Franc and the UK Pound) weakened significantly relative to the US Dollar. As a result, as of 31 December 2014 MMV booked an unrealized foreign exchange loss of USD 1.3 million. In January 2015 the Swiss Franc strengthened considerably against the US Dollar and most currencies.

11. LEASES

Non-cancellable operating lease rentals are payable as follows:

	2014 USD	2013 USD
Less than 1 year	919 654	846 666
Between 1 and 5 years	2 240 648	2 900 918
More than 5 years	–	–
TOTAL	3 160 302	3 747 584

MMV has several operating leases. These leases generally run for a period of 5 years, with an option to renew the lease after that date. During the year ended 31 December 2014, USD 920,577 were recognized as an expense in the Consolidated Statement of Comprehensive Income in respect of operating leases (2013: USD 831,881).

12. CONTINGENT ASSETS

As per current contractual agreements, and depending on satisfactory reporting to donors, contingent assets related to donations are as follows:

	2014 USD	2013 USD
Less than 1 year	74 331 769	66 715 000
Between 1 and 5 years	133 256 162	189 524 000
More than 5 years	–	–
TOTAL	207 587 931	256 239 000



13. RELATED PARTIES

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

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

BOARD MEMBERS	2014 USD	2013 USD
Board members and meetings	172 950	158 789

There were no loans to directors or executive officers for the years ended 31 December 2014 and 31 December 2013.

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

14. RISK MANAGEMENT

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

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

15. GUARANTEES

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

16. CAPITAL COMMITMENTS AND CONTINGENCIES

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

17. SUBSEQUENT EVENTS

No events have occurred between balance date and the date of this report that require adjustment to, or disclosure in, these financial statements. ●



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Report on summarized consolidated financial statements to the management of
Medicines for Malaria Venture, Geneva

We have audited the financial statements of the Medicines for Malaria Venture for the year ended 31 December 2014 from which the summarized financial statements were derived, in accordance with Swiss Auditing Standards and with the International Standards on Auditing. In our report dated 12 March 2015, we expressed an unqualified opinion on the financial statements from which the summarized financial statements were derived.

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

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

KPMG SA

Pierre-Henri Pingcon
Licensed Audit Expert
Auditor in Charge

Sylvain Perrière
Licensed Audit Expert

Geneva, 12 March 2015

Enclosure:

- Summarized financial statements

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