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Medicines for Malaria Venture (MMV) is a not-for-profit organization dedicated to reducing the burden of malaria in disease-endemic countries by discovering, developing and delivering new affordable antimalarial drugs through effective public-private partnerships. Our vision is a world in which these innovative medicines will cure and protect the vulnerable populations at risk from malaria, and help to ultimately eradicate this terrible disease.

Medicines for Malaria Venture has received funding and support from the following organizations:


MMV is also very grateful for the support it has received from a number of private individuals.
The challenging path to eradication

If there ever was a golden age for malaria innovation, it is now. In 2007, we commented on the need for the malaria community to set audacious targets if the ambitious goals of elimination and eradication were to be achieved. The unprecedented momentum that had grown out of this “call to arms” resulted in an excellent pipeline of new antimalarial drugs and vaccines, with MMV leading the way. As 2008 drew to a close, the pre-eminent journal Nature called it a watershed year, marking it as a turning point in malaria control.
THE CHALLENGING PATH TO ERADICATION

A successful team beats with one heart and also beats the odds. As we review MMV’s contribution to malaria innovation, we can be justifiably proud that 2008 was a year of incredible teamwork, a year in which, most notably, we and our pharmaceutical partner Novartis completed the registration of Coartem® Dispersible to stringent international regulatory standards. This achievement is not just a first for MMV, but for all Product Development Partnerships (PDPs). The data supporting the registration is clear and compelling and it was therefore not surprising that MMV’s External Scientific Advisory Board (ESAC) unanimously judged Coartem Dispersible to be MMV’s Project of the Year 2008.

The parent drug, Coartem® was also in another significant MMV success story in 2008 – namely the launch of a pilot study conducted with the Ministry of Health in Uganda. The study provided Coartem as the heavily-subsidized Artemisinin Combination Therapy (ACT) via the private sector supply chain. The thinking, design and early experience from this pilot proved catalytic in the decision made by the Global Fund to fight AIDS, TB and Malaria (GFATM) to host the Affordable Medicines Facility, malaria (AMFm), a mechanism designed to increase the overall use, affordability and availability of eligible, good quality ACTs.

Despite Coartem Dispersible and other important scientific achievements detailed in this report, not all was plain sailing in 2008. MMV was tangentially affected by the financial storm that continues to depress global economic activity. In some ways we were fortunate compared with other sectors of the economy, but no organization that operates contractually in four currencies, and has a treasury function to manage retained capital, could have been wholly spared.

While acknowledging the economic downturn and the increased risks that inevitably come with it, we did not let this stop the momentum and enthusiasm that had been built in the past year. We did all we could to mitigate the risk. For example, MMV decided to consolidate and increase fundraising capacity by creating a department for Corporate Development that is both fully integrated into the senior management team and able to draw on the experience and advice of a dedicated MMV Board sub-committee.

In addition, on 25 September 2008 we launched our new 5-year Business Plan, which is a plan for growth and increased organizational capacity. The most notable variance between this and earlier plans is that it squarely places MMV’s drug innovation and delivery work in the framework of a global malaria eradication strategy. It is, thus, not a coincidence that MMV’s Business Plan was formally launched on the same day as the Roll Back Malaria (RBM) Partnership’s Global Malaria Action Plan (GMAP), which sees malaria eradication as its central, albeit long-range, goal. The next few years will be the first time in at least half a century that the expertise and strategies of all the major actors in the malaria research and control community will be aligned under a common mission. Bringing about this alignment was no mean task and due credit must be given to the leadership of the RBM Partnership Board and the many individuals who supported this work.

According to GMAP analysis, USD 750-900 million a year would fund all global product and operational R&D for the next 10 years. MMV’s Business Plan estimates a need for approximately USD 75 million per year, representing ~10% of the GMAP total. This relatively modest percentage does, however, make the point that MMV’s costs are, by any comparator, good value for money. For instance, with the partnership model, we have already developed and launched one drug at a highly reduced cost compared to industry estimates to do the same. In parallel, we have built a quality pipeline – the equivalent of which might be valued at a significant premium to its cost if our products were commercially costed.

In spite of the complex global financial environment and the fact that we are integrating our work into a larger global picture, our traditional core R&D activity is well navigated and understood. This is not always the case for our Access and Delivery work. Here, a one-size-fits-all approach simply does not work. Understanding market structures and the kinds of medicine people are able to access is not a uniform undertaking for all of sub-Saharan Africa. Barriers to accessing high quality ACTs have many causes, and vary considerably from one country to another. A good understanding of the specific local dynamics is indispensable.

As an example, the level of country-based detail needed in our Uganda ACT pilot required us to create a Ugandan legal entity to support it. Moreover, market information from one country cannot automatically be generalized to another, within the same sub-region or to other malaria-endemic regions, such as sub-Saharan Africa, South America and South East Asia.

As we expand our Access work, we will have to work with many local partners and face the challenges of local politics. Our aspiration is to facilitate the supply of the best and most affordable products, leading first to a reduction of the malaria burden and ultimately to its eradication.

This will help patients and save many lives, but will undoubtedly contest those with an economic interest in cheap, poor quality, antimarial drugs. This is all the more reason to engage with these complexities sooner rather than later.

Most worthwhile goals are hard to achieve, and their accomplishment often goes unsung. Our Access work is no exception. As we reach our milestones, we are encouraged by the comment of a distinguished American, the author Mark Twain, who noted that: “There are basically two types of people. People who accomplish things, and people who claim to have accomplished things. The first group is less crowded.”

We can justifiably be proud that 2008 was a year of incredible teamwork – a year in which much was achieved in terms of science and access.
SUCCESS HIGHLIGHTS

Building the pipeline

MMV has built a robust pipeline of almost 50 antimalarial drug projects over 9 years.

Preparing the launch

MMV has three new combination therapies in late-stage clinical development, with one approved by a stringent regulatory authority and ready for launch.

Current Portfolio Financial Allocation – USD 40.3 million

MMV’s balanced portfolio places greater emphasis on discovery research and late-stage clinical development.

MMV Funding 2000–2012 from 14 donors – USD 330 million

MMV Expenditure 2008 – USD 55.8 million

Almost 90% of MMV’s resources supports the discovery, development and delivery of effective new antimalarials.

Facilitating access and delivery

Market Survey Report

MMV’s first Market Survey Report was published in August 2008. This summarized the findings from a study of the antimalarials market in Uganda, including: market structure in the private and public sector; costs, availability and affordability; and supply chain and price mark-ups.

Launch of CAPSS Programme in Uganda

On 19 September, MMV and the Ministry of Health (MoH) Uganda launched a joint initiative in partnership with the Consortium for ACT Private Sector Subsidy (CAPSS) to deliver a heavily-subsidized ACT (Coartem®) to the rural poor via the private sector. The launch event was inaugurated by the Prime Minister of Uganda, Rt. Honourable Apollo Nambiti. CAPSS is led by the MoH and MMV, and comprises local partners with valuable experience in malaria prevention and treatment, including the National Drug Authority, Population Services International (PSI), Surgipharm, Malaria Consortium, and International Dispensary Association (IDA) solutions.
ADVANCES IN ACCESS

Dismantling barriers, consolidating gains

MMV’s Access work represents a small but critical part of our current resource allocation. It responds to the belief that an exclusive focus on discovering and developing new antimalarial drugs is not enough; the organization and its stakeholders must also facilitate the delivery of new quality therapies to those who need them the most.

In 2008, MMV consolidated work that the fledgling Access team began putting in place over two years ago, culminating in important breakthroughs in our market intelligence efforts and in our support for promoting ACT subsidies in the non-premium private sector. It was also a year of intense support and planning for the exciting anticipated launch in early 2009 of MMV’s first product, Coartem® Dispersible, jointly developed with our pharma partner Novartis. Lastly, in anticipation of two additional product registrations by 2010, the team has been expanded to address the new challenges and opportunities that will open up in the coming years.
Dismantling Barriers, Consolidating Gains

Barriers to Access

Much of our Access work can be linked to barriers to access and correct usage that were identified and validated when MMV first started to focus on this area of work. There are several barriers to the access and correct use of antimalarial medicines, such as ACTs. These are described in a little more detail below.

Geographical and health system barriers

Across Africa, countless people seek cures for malaria outside of the publicly-funded national health systems. Although the percentage might vary from one country to another, the number appears to range from 40-60%. The phenomenon is partly explained by geographical barriers, which make it difficult for patients to get timely access to public health facilities when fevers occur, partly by the fact that private-sector outlets are closer at hand, and partly by the frequent failures of many health systems to consistently and adequately stock effective medicines that patients need.

Purchasing power barriers

Whilst most countries provide free treatment within the public health system, patients who elect or are forced to seek treatment outside of the health system pay for their treatment out of their own pocket. Thus, the economics of spending power make it difficult for patients to pay for full doses of effective quality medications, forcing them to buy unsuitable, unregulated, ineffective treatments, or partial dosages of effective treatments.

Information barriers

There is stunning ignorance about just how the public supply systems and private marketplaces work in many African countries. To date, it is difficult to pinpoint accurately the true root causes of public system failure to deliver ACTs, even when necessary funding is available.

In the private sector, very little has been done to either quantify the volume of good versus bad drugs flowing through the system, or to devise commercial strategies that could push out bad drugs by making good drugs enticing for distributors and affordable for patients.

Barriers to correct training and appropriate usage

Effective and appropriate training of public health caregivers must be improved, to ensure that patients are correctly treated and that good medications are not weakened through inappropriate use. When medicines are purchased in the private sector, often without the advice of trained medical personnel, one must ensure that patients understand how to take treatments fully and correctly.

Consolidating Gains

In both public and private sector settings, the frequent lack of proper diagnosis to confirm malaria means that every year millions of cases of non-malarial fever are treated presumptively and incorrectly with antimalarials.

Launch of CAPSS

Prime Minister Apollo Nsibambi inaugurated the CAPSS study in Uganda. This was the culmination of a high-energy collaboration between MMV, the MoH and CAPSS partners over the course of 18 months. This two-year pilot is studying the impact of an innovative subsidy to make effective antimalarials (Coartem, in this case) available in the private sector at prices that can compete with older, ineffective, but still popular drugs such as chloroquine or sulphadoxine-pyrimethamine.

The CAPSS experience was one of the supporting pieces of evidence presented to the Global Fund Board as the Board weighed the evidence for, and ultimately approved, the ARm.

First results of MMV’s Market Intelligence work

As part of its focus on understanding the dynamics of the marketplace into which MMV products will be launched, the Access team released its first market report, Understanding the Antimalarials Market: Uganda 2007, providing new insights into the local antimalarial market in nine rural districts in Uganda. This report (fig. 1 below), provides a detailed view of the myriad cheap and ineffective products poor Ugandans are confronted with when seeking self-treatment for suspected malaria. It also shows how inaccessibly priced are the quality ACTs that they would ideally take if they could afford them. This study offered useful evidence in guiding the MoH Uganda’s decision to subsidize the cost of ACTs via the CAPSS pilot. MMV is working on a number of other key market intelligence initiatives to understand the structure, size and drivers of the antimalarial markets in key African countries.
Global Fund Board approval of the Affordable Medicines Facility, malaria (AMFm)

In 2004, an influential report by the US Institute of Medicine called for the creation of an international subsidy that would enable poor people to afford effective antimalarial treatments such as ACTs. It was a recognized fact that the most vulnerable would need a radical reduction in the price of these essential medicines if they were to gain access to malaria treatment.

Developing the AMFm from a mere concept into a practical, workable model has required an enormous amount of energy by multiple stakeholders. The AMFm will be the first internationally-coordinated attempt to systematically dismantle the prohibitive cost barriers that have kept ACTs out of the hands of millions of patients who desperately need these life-saving drugs.

Coartem Dispersible registration and launch preparations

The timely submission of the Coartem Dispersible dossier to the Swissmedic regulatory authority in 2008 signifies a historic moment in the life of MMV – a moment that represents the culmination of years of works.

MMV’s Access team contributed significantly to the preparation and testing of patient-friendly packaging and the development of training materials for health workers. This is critical to ensuring correct dispensing and use of this paediatric Coartem formulation. In addition, in anticipation of product approval, MMV worked in tight collaboration with Novartis throughout 2008 to begin planning a successful launch of the product in 2009.

Looking forward, MMV Access will face an exciting and challenging year in 2009. The scale-up of Coartem Dispersible will be linked to our ongoing efforts to assure that this and other quality medicines are as widely available as possible throughout the public and non-premium private sectors.

There will be new opportunities to expand access to Coartem Dispersible through programmes designed to deliver correct diagnosis and treatment of malaria via community health workers in rural communities. Also, as advances occur in reducing the costs of rapid diagnostic testing and making diagnostic tests more widely available, we will support strategies that seek to couple correct diagnosis with treatment of malaria.

Lastly, we remain firm in our belief that unless MMV and the global malaria community improve the ability to routinely measure public health system performance and private sector channels that deliver quality antimalarials to patients, we will be working in the dark without a true understanding of whether these drugs are truly saving lives.

MMV is proud to have been closely aligned to efforts to set up the AMFm, which will help dismantle the cost barriers that have kept ACTs out of the hands of the millions that need them.
Of the hundreds of thousands of children who lose their lives to malaria each year, most are under the age of five and live in sub-Saharan Africa. In this part of the world, nearly one in five of all children who die so young are killed by malaria. The lives of children are being held at ransom by this relentless disease.

We all know that malaria is a disease of poverty and are aware that the consequence of this waste of young lives on families and communities is yet more poverty. People in malaria-endemic countries will be unable to escape this poverty trap and stop the decimation of their children’s lives unless malaria is tackled head on. The world needs to urgently intervene to stop the deaths of the very young.

Children are the hardest hit

Children and Malaria
The malaria parasite is a lethal foe. Without prompt and effective treatment a child can die within 24 hours of onset of symptoms. But death is not the only appalling outcome. As children’s immune systems are still immature and they have not yet developed sufficient naturally-acquired immunity to the parasite, the non-lethal effects of malaria on children under five can be extraordinarily debilitating. Statistics tell the story with pitiless brevity:

- Malaria kills a child every 3 seconds i.e. around 2,500 children die each day.
- This year, over 700,000 children under five will die from malaria.
- Infants born to mothers with malaria are more likely to have low birth weight — which is widely believed to be the single greatest risk factor for death during the first month of life.
- Malaria is the cause of nearly 20% of low-birth weight babies in malaria endemic regions.
- Severe malaria often leads to cerebral damage, holding back a child’s mental development.
- Malaria contributes heavily to malnutrition, an underlying cause of more than half of all deaths in children under five.

Uncertainties of malaria control
The most unpalatable fact underlying this litany of statistics is that malaria is an entirely preventable and curable disease.

The use of insecticide-treated bednets, indoor residue spraying with insecticides and environmental measures such as the draining of stagnant pools of water, go a significant way to preventing malaria. But unfortunately, these are not enough. Although the female anopheles mosquito is known to bite mainly after sundown, there is no certainty that bites will not occur earlier in the day, nor is there any certainty that all children will be tucked into their net-covered beds by sundown. Insecticides used for indoor spraying of houses kill mosquitoes but, poorly used, have adverse effects on the health of human beings. Research is currently underway to develop new insecticides that are less toxic to humans and more ecologically friendly.

But what about MMV’s area of innovation: medicines?
Most antimalarial medicines available in the poorer rural areas of Africa, for instance chloroquine and sulphadoxine-pyrimethamine (SP) are largely ineffective. Newer, strikingly effective medicines such as ACTs are sold privately at unaffordable prices. Thus, caregivers and parents are often confused — how should they spend their hard-earned money? On the one hand, drugs they can afford, but that are practically useless at curing their children of malaria? Or just a portion of a more expensive but effective treatment? Or should they spend time and money going to a public clinic where treatment might be free, only to find it is no longer available? Cost is the critical consideration because of abject poverty.

To complicate matters, caregivers are often given antimalarials for their child’s fever, whether the fever is malarial or not. More often than not, they are given cheap antipyretics for malarial fever, which can be fatal as the malaria is left untreated. What would be useful is a reliable, affordable diagnostic test to first check for malaria; but this would inevitably add to the cost of treatment.

Then there is the question of how to ensure that the child swallows the entire dose and is not under-medicated. Under-medication not only leads to lowered drug efficacy but to potential parasite resistance. Moreover, many standard tablets have to be crushed before they can be given to infants and young children; these are often spat or vomited out because of their bitterness. To make matters worse, caregivers are never certain that the precious tablets they buy for their children are not counterfeits.

First obvious intervention
If we are to make a dent in the grip that malaria has over significant regions of the developing world, and take the first step towards eradicating this disease, we must prioritize ways to treat children. The global community might have a number of effective interventions to tackle malaria, but new ones are urgently needed to target treatments towards this most vulnerable patient population. We need high quality, safe, affordable and effective medicines designed especially to treat and prevent malaria in children.

It is an uphill task to overcome the many challenges outlined above, but the journey can be tackled one step at a time. To meet the challenges, the first MMV-supported paediatric formulation, Coartem Dispersible (pages 26 and 40), has been approved by a stringent regulatory authority (Swissmedic), and launched in early 2009. It has also been approved by 14 regulatory authorities in Africa. These countries include Benin, Burkina Faso, Democratic Republic of Congo, Gabon, Ghana, Guinea, Ivory Coast, Kenya, Madagascar, Mauritania, Niger, Nigeria, Senegal and Togo. Other countries are expected to be added to this list soon.

Next daunting challenge
Although Coartem Dispersible will be provided at cost to the public sector in malaria-endemic countries, most of the public health systems in these countries need restoring. A common problem is stock-outs of drugs in public sector facilities, leaving patients to buy medicines from the private sector. How can we ensure that the medicine will be affordable to vulnerable patients? Can public health delivery systems be strengthened to ensure that ACTs are always available when patients need them? How can we activate additional help, such as from community health workers, to increase access to life-saving drugs? MMV is working in the area of Access to remove obstacles and facilitate the delivery of effective ACTs to outlets most commonly used by poorer people.

MMV’s aim is to ensure that no child should have to choose between health and hunger; no caregiver should have to choose between the life of their child and the pennies in their pocket.
A new era begins

In 2008, MMV entered a new era of drug discovery and development – targeting not only malaria treatment but also its ultimate eradication. Our portfolio of novel medicines has continued to develop, and now, one year after a renewed call for malaria eradication went out to the malaria community, is a good time to review the status of this portfolio.

Artesunate: The artemisinin component within the ACT Pyramax.
Novel medicines

One of the most exciting developments in 2008 was Swissmedic's approval of Coartem® Dispersible (Coartem-D), a new, child-friendly, fixed-dose artemisinin combination therapy. With its dispersible formulation that avoids the need to crush tablets, and its carefully selected flavour that masks the bitter taste of the parent drug, Coartem®, we believe this therapy will have a major impact on the lives of over 45 million children worldwide. Awarded MMV's Project of the Year 2008 (page 40), Coartem Dispersible is our first product, developed in partnership with Novartis; it is now ready for distribution and will be launched widely in 2009.

Over the last year we have also been busy running four major Phase III studies on Pyramax® (pyronaridine-artesunate), in collaboration with Shin Poong Pharmaceuticals in Korea and Professor Larry Fleckenstein at the University of Iowa. Four trials were run in parallel:

- Two against current therapy for Plasmodium falciparum infections;
- One against current therapy for Plasmodium vivax infections; and
- One with a specific paediatric formulation.

Results are currently being analyzed and, all being well, we hope to submit the Pyramax dossier to stringent regulatory authorities in mid-2009.

Our third late-stage project was the development of Eurantems® (dihydroartemisinin-piperaquine), in partnership with Sigma-Tau Industrie Farmaceutiche Riunite in Rome, Italy. Given that we were aiming for a very high quality end product that would be stable for as long as three years in hot and humid conditions, the choice of formulation was very important and a considerable amount of work went into generating the final product. Clinical trials are now complete, and we are in the process of analyzing results.

As well as proving that new medicines are more efficacious than previous ones, drug developers need to show that each new medicine is at least as safe as the last. We were reminded of this challenge through our experience with Dacart™ (chlorproguantidipasone-artesunate), a final Phase III project in partnership with GlaxoSmithKline (GSK). Dapson was known to increase the risk of haemolysis (red blood cell destruction), in some African patients who are deficient in G6PD (a metabolic enzyme). We therefore compared Dacart with Coartem, the current standard treatment, in two large clinical trials. These showed far more adverse events in the Dacart group – a result that led to GSK’s decision to terminate the project. This was extremely disappointing as several years’ work had gone into Dacart, but the excellent trials and quality of the data enabled us to make a clear decision in Phase III.

Translational medicine

Research on compounds and molecules from the start of regulatory preclinical development through to demonstration of clinical activity in patients (translational medicine) has been a key area of growth in 2008. As with any pipeline, the growth comes from two areas: first, the progression of existing MMV-supported activities, and second, the identification of new and promising external projects.

Following on from work with GSK, we are now ready to start human volunteer studies on the first generation of 4-aminoquinolines. Meanwhile, from our partnership on oxonide molecules, preclinical evaluation of the second generation molecule OZ-439 was completed in record time. Phase I trials are scheduled to start in early 2009.

MK-4815, a new molecule from Merck & Co that is ready for Phase I trials, and studies on the pure diastereoisomer of Mefloquine, are interesting proteges that have arisen externally. We have also completed negotiations with early-stage partners for discovery, and have signed a memorandum of understanding with sanofi-aventis (who have three novel chemical entities at different stages of clinical development); this takes the number of MMV’s collaborations with top-ranking pharmaceutical companies to five.

Malaria eradication

New medicines to help us meet the challenge of malaria eradication are now at the forefront of our thinking. In 2008, we focused on strengthening the portfolio with new approaches to Plasmodium vivax, in particular to its dormant liver stage known as the hypnozoite. Our most advanced project here is Tafenoquine™, which we know has activity against hypnozoites. But, like dapsone, Tafenoquine causes increased haemolysis in people with G6PD deficiency. The challenge is to find a safe dose; this safety study will commence in 2009. In parallel, we have started a preclinical programme with the antibiotic Minimycin™ (shown to work against hypnozoites in preclinical models); meanwhile two of our identification partners are making great progress on producing a cell-based assay for hypnozoites.

Another challenge of malaria eradication is to find ways to break the transmission cycle. One solution is to develop medicines with increased activity against the gametocytes, or sexual stages of the parasite. We are actively working on setting up high content screening assays for compounds that can kill gametocytes. If we can prevent gametocyte production, then we can prevent the infection of the next generation of mosquitoes and so break the infection transmission cycle. We will be able to report more on this next year.

Drug discovery pipeline

Our discovery effort has grown rapidly (page 22, MMV Discovery Portfolio). We aim to have enough early-stage drug discovery projects to allow us to bring two or three high quality molecules into preclinical development every year. In theory, this should allow us to launch a completely novel combination therapy every five years.

A number of ‘Mini-portfolios’ (collaborations with major drug discovery units) have been developed to this end: with GSK in Tres Cantos, Spain, Novartis in Singapore and San Diego, USA, and the Broad Institute and Genzyme in Boston, USA. We hope to build many more such collaborations over the next few years.

We have also built excellent partnerships with academic centres, strengthened by our 6th Call for Proposals which received over 100 high quality proposals. Many of these focused on defined targets, and we have been able to start the process of matching up new targets with industry groups interested in screening them.

Integrated technologies for the eradication era

The landscape of basic discovery has changed radically over the last two years, thanks to cutting-edge technologies. High content screening has allowed us to screen almost 4 million compounds for their ability to kill parasites. Development of a 384-well assay (by the Eskitis Institute in Queensland, winners of MMV’s Project of the Year 2007), means it is now easier to screen smaller collections of compounds (e.g., from academic groups or smaller biotech companies). This is already beginning to provide interesting starting points for medicinal chemistry.
Our People

Finally, we should emphasize that the strength of any organization lies in the calibre of its people. As well as its internal staff, MMV is fortunate to have a wide range of world class experts in its Expert Scientific Advisory Committee (ESAC).

This team was reinforced with many new members in 2008, specifically focusing on drug development and clinical aspects.

Meanwhile, we were sorry to say goodbye to Dr Winston Gutteridge, who chaired the ESAC ably and courageously over the last six years; our sadness is lessened by the fact that he will be joining the MMV Board, so it is really only au revoir.

The robust antimalarial drug discovery and development pipeline that MMV has managed to build to date is a clear reflection of the commitment of all our advisors, colleagues and friends over the last 10 years, who have given their experience and expertise freely to help discover, develop and deliver new medicines for malaria.

MMV Discovery Portfolio 2008 – Fourth Quarter

LEAD GENERATION

HTS Workup, GSK
HTS Workup, Broad/Genzyme
Natural Products, Broad/Genzyme
GNF Screening, Novartis
Liver Assays, Novartis
Natural Products, Eidav
GnomeScreen, Celldex
Natural Products Screen, Eidav/DPP
SF Library Screen, Eidav
Liver Assays, SBI
Kinase Screen, Dundee
Natural Products, USF
DHODH, GSK
HSPPS, Broad/Genzyme
DHODH, Broad/Genzyme
HDAC, Broad/Genzyme
Kinase Hit, Novartis
Heterocyclic, NH-4-Label, TDIY/Pharmassence
Immucillins, Albert Einstein
Quinolones, USF

LEAD OPTIMIZATION

THQ, GSK
Aminobenzenes, Broad/Genzyme
Whole Cell Leads, Novartis
DHODH, USTW/Unimark
Falcipains, GSK
IPT Pyridones, GSK
Macrolides, GSK
DHFR, BICTEC/Monash/LHSTM
Oxazoles, Monash/Unimark/USF
KAC776, Novartis

MMV Portfolio 2008 – Fourth Quarter

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<sup>1</sup> Lead generation project details are shown on page 22.
<sup>2</sup> Lead optimization project details are shown on page 22.
<sup>3</sup> With stringent international regulatory authority.
Today, MMV has over 50 projects in discovery, preclinical and clinical development – the most robust and diverse portfolio of antimalarial drug projects in history. Two clinical development projects are close to registration, while at the other end of the pipeline 19 completely new classes of drugs are being investigated in early-stage discovery. The discovery portfolio consists of 30 projects, most of which are grouped together in Mini-portfolios. MMV is focusing its efforts on progressing the projects in the discovery portfolio through to the preclinical phase.
Coartem® Dispersible (artemether-lumefantrine) dispersible tablets — Approved

Novartis and MMV have completed the development of a paediatric dispersible tablet containing a fixed-dose combination of artemether and lumefantrine for the treatment of *P. falciparum* malaria. To mask the bitter taste of the active ingredients, this medicine has a cherry flavour — chosen after studies with African children. The course of treatment is twice-a-day over three days. This product is easy and cost-effective to manufacture and, aside from a few additions to the pictorial instructions to encourage responsible use, will retain the well-known WHO package format currently used by Coartem.

The regulatory dossier was submitted to Swissmedic in December 2007, based on clinical data comparing the dispersible formulation with the original Coartem. The drug was approved by Swissmedic in December 2008, and has already been approved in 14 malaria-endemic countries (with approvals pending in a number of others). The product, which we consider to be the product of choice for children, will be officially launched in these countries in 2009.

Pyramax® (pyronaridine-artesunate) — Phase III

Pyramax is a fixed-dose combination of artesunate with the 4-aminoquinoline pyronaridine. It is being developed as a once-a-day for three days treatment for uncomplicated *P. falciparum* and *P. vivax* malaria. In 2008, we completed four pivotal Phase III trials involving a total of 3,533 patients in 18 countries. In all cases, the trials achieved their primary endpoints of non-inferiority compared with current standard of care at 28 days.

The first study, in sub-Saharan Africa, compared Pyramax with artemether-lumefantrine in 1,273 patients with uncomplicated *P. falciparum* infection. This study was completed in the third quarter of 2008. The second study compared Pyramax with artesunate + mefloquine in South-East Asia; this was also completed around the same time. Given the increasing importance of *P. vivax* in the eradication agenda, a specific trial compared Pyramax with chloroquine in 406 *P. vivax*-infected patients. This trial was completed in the last quarter of the year.

Finally, the paediatric granule formulation of Pyramax is being tested for safety and efficacy in young children and infants (with a body weight of between 5 and 25 kg). The large amount of clinical data and number of patients to be recruited means that we now anticipate filing for registration with the EMEA (the European Medicines Agency) in the summer of 2009. Our pharmaceutical partner in this project, Shin Poong Pharmaceutical Co. Ltd., Seoul, South Korea.

Eurartesim® (dihydroartemisinin-piperaquine) — Phase III

Eurartesim is a fixed-ratio drug combination being developed in partnership with Sigma-Tau Industrie Farmaceutiche Riunite, in Rome, Italy, to treat uncomplicated *P. falciparum* malaria. Piperaquine is a 4-aminoquinoline with an extremely long half-life, so this combination is expected to be effective both in treating clinical malaria and in giving protection from re-infection.

The clinical part of the two pivotal, controlled, double-blind Phase III trials were completed in 2007. The first trial, in South-East Asia (India, Laos and Thailand) recruited 1,150 patients and used artesunate + mefloquine as the comparator. The second trial involved 1,533 patients in five centres in Africa (Burkina Faso, Kenya, Mozambique, Uganda, and Zambia) using artemether-lumefantrine as comparator.

Over the last year we have been analyzing the clinical data and preparing all the formulation and stability data. These are being collated to produce the regulatory submission, which will be filed with the EMEA under the Orphan Drug Regulation in the summer of 2009. Currently, no specific formulation or dosage of Eurartesim exists for use in small infants or in expectant mothers. We will be working to select a specific formulation of this medicine for small infants in 2009. In addition, we have started the regulatory preclinical safety and toxicology studies to test the medicine in expectant mothers, with a view to finding the optimal dose for this patient group.
The haematocrit measures how much space of Hygiene & Tropical Medicine, UK
University of liverpool, UK; liverpool School of WHO Special Programme for Research and Training Partners
Drug Development and Discovery Projects

In 2008, we completed two pivotal Phase III clinical trials in adults and children in Africa. The first study compared Dacart and Coartem. The second compared Dacart with chlorproguanil-dapsone. There was a key need to find out how safe Dacart was in patients lacking the G6PD enzyme, since there was a concern that it could lead to increased lysis (destruction) of red blood cells. Both studies were a success, in that the primary end-point of clinical efficacy was achieved. There was a slight increase in the loss of haematocrit* for patients on Dacart compared with those being treated with Coartem. When the G6PD-deficient subgroup (corresponding to 15% of the patients) was sub-selected, the safety concern was even larger. All of the serious adverse events (requiring blood transfusion) occurred in the Dacart group.

Any medicine being used in a malaria-endemic country has to have an extremely good safety profile, since processes are less well-developed for reporting and monitoring adverse events once the drug is available to the public at large. On the basis of the safety data, the project team recommended that work on the submission of the dossier to the regulatory authorities be discontinued. On the positive side, GSK has made available the enormous amounts of data on the clinical studies; this has streamlined some of our discussions on other artesunate-containing therapies.

Intravenous artesunate – Phase II

In collaboration with the University of Tübingen, we are conducting a Phase II study in Africa on the effects of intravenous artesunate in the treatment of severe P. falciparum malaria. The study has recruited 200 patients, and will compare two different treatment regimens using GMP-quality artesunate provided by WRAIR (Walter Reed Army Institute of Research, USA). The major issue identified by ESAC was the long time taken to produce artesunate under GMP conditions. This will be the focus of discussions in 2009.

Artemisone – Phase II

Artemisone is an N10-substituted artesinin derivative identified by the University of Hong Kong Institute of Science and Technology (U-HKIST), and developed in partnership with MMV and Bayer. This project had been put on hold as Phase II data had not shown significant superiority over other artesinins, but recent reports of patients who are refractory to treatment with artesinin (i.e., longer parasite clearance times) have brought artemisone back into the pipeline. However, parasites that are less responsive to artesinin in culture have not yet been identified.

Tafenoquine – Phase I

Tafenoquine is our lead project specifically aimed at targeting a radical cure of P. vivax infection. It is an 8-aminoquinoline, of the same family as primaquine, and is known to have activity against hypnozoites (the dormant liver stages of the vivax parasite). However, tafenoquine has the potential advantage of having a much shorter treatment period; this should result in increased patient compliance. The project was approved in December 2007, and since then has been spent designing the clinical packages and producing the material for trials.

The first clinical study will be an ascending dose safety study in G6PD-deficient heterozygotes, with a view to identifying the maximum safe dose. At an expert panel meeting in 2008, the development of a loose combination rather than a fixed-dose combination was recommended of tafenoquine with either chloroquine for regions where P. vivax is chloroquine-sensitive or with an ACT where P. vivax is chloroquine-resistant. These drugs would be explored as potential partners in clinical drug-drug interaction studies, which will commence in 2009. Phase II dose-ranging studies on the combination therapy are currently planned for 2010. We are currently exploring the possibility of combining the Phase II and III studies into an integrated trial design, with a view to bringing forward the date for submission to the regulatory authorities.

Isoquine (GSK 369796) – Phase I

N-tertiary butyl isouquine (GSK 369796) was being developed in partnership with GSK and the University of Liverpool, where it was designed. The compound was based on the antimalarial emodioquin, but had been re-designed to eliminate the liver toxicity of aminooquinolines, while retaining full antimarial activity.

The Phase I single ascending dose study was started in May 2008, and volunteers were tested with doses as high as 1,000 and 2,000 mg. An adverse event was seen in the highest dose, and the plasma exposure was lower than expected, effectively lowering the safety window to a level where the project team decided that the risk of continuing the study was too high. This led to the Phase I trial being discontinued. Based on this, and other safety considerations, MMV’s ESAC recommended in November that the project be terminated. As a result of this project, we now have a much larger database of preclinical safety data on 4-aminoquinolines. This will help us in the future, since there are still other 4-aminoquinolines in development outside of MMV.

We are currently screening existing ozonide and artesinin compounds against Plasmodium isolates from patients in areas where increased parasite clearance time has been reported. The question that arises now is: When resistance emerges, will it only be against artesinin, or will the entire class of ozonides be at risk? In parallel, we are investigating the activity of new generations of artesminins (those with an IND*) to see if they have a differential effect in patients. This study is being carried out in collaboration with Mahidol University, Thailand.

* The haematocrit measures how much space in the blood is occupied by red blood cells. It is useful when evaluating a person for anaemia.

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PRECLINICAL DEVELOPMENT PROJECTS

GSK 932121A

The 4-pyridone class of inhibitors is a potent antimalarial class of agents. The mechanism of action involves blocking the electron transport chain in the parasite mitochondrion. A number of interesting compounds have been produced by our partners, GSK at the Diseases of the Developing World Centre in Tres Cantos, Spain.

In December 2006, the compound GSK 932121A was selected for preclinical development based on the fact it was highly potent and had better physicochemical properties and pharmacokinetics than other members of this class.

The molecule has successfully completed the necessary preclinical safety and toxicology studies. Phase I studies are scheduled to start in the spring of 2009. In parallel, a pro-drug has been developed with a major increase in solubility, and we are currently optimizing this as part of the GSK Mini-portfolio.

OZ 439

MMV has had a long-standing interest in synthetic peroxides, working in collaboration with the University of Nebraska Medical Center, USA, Monash University, Australia, and the STI. The first clinical development candidate, OZ 277, was found to be relatively unstable due to high plasma iron levels in patients. The next candidate, OZ 439 was designed specifically to overcome this problem. It maintains a high potency with increased iron exposure in model systems, and based on current model data we predict that this will be a very active molecule given as a three-day treatment. It also holds promise of activity as a single-dose treatment.

The OZ 439 project team completed the preclinical work in 2008, and is ready to start the ‘first in human’ studies in the spring of 2009. The project – from candidate selection through to demonstration of efficacy in patients – will be run internally by MMV. Detailed studies will be managed by Fulcrum Pharma (Europe) Ltd, UK. Since we have to combine at least two active ingredients in each new medicine we produce, it is important for our portfolio to include some drugs which do not have a pharmaceutical partner. This will give us additional flexibility in the future.

MK 4815

A new addition to our portfolio, the molecule MK 4815, was discovered in whole parasite screens carried out at Merck & Co. It is potent against P. falciparum malaria when tested in vivo, and is currently going through the later stages of safety pharmacology. The aim was to have the first administration in humans by the end of 2008.

MK 4815’s mechanism of action appears to include action on the mitochondrial electron transport chain of the parasite, and the molecule has been shown to be actively concentrated in infected erythrocytes. This mechanism targets the molecule to the site of action and minimizes side effects.

Preclinical toxicology and safety studies have been completed. Meanwhile Merck & Co have signed an agreement transferring the project to MMV. It will now be run internally – through to demonstration of activity in patients – by MMV. The first-in-human studies are expected to start in the summer of 2009.

(+) Mefloquine

Mefloquine is a long-acting antimalarial composed of a mixture of diastereoisomers*. Both (+) and (-) isomers of mefloquine are active antimalarial agents, but some central nervous system (CNS) side effects (sleep disorders and depression) are thought to be related to the (-)-erythro isomer.

The focus is therefore on the (+)-erythro isomer; this has already been tested in a Phase Ila study for its anti-inflammatory properties. We are currently collaborating with Treague, who own the rights to the Phase Ila data, to design a Phase I study to confirm that the pure (+)-erythro isomer does not induce CNS side effects, and gives good exposure, or high enough levels in the blood and other target organs, for the drug to exert its desired antimalarial effect at the doses that are expected to be required for malaria treatment. We plan to start the Phase I safety study in the first half of 2009.

Mirincamycin

Mirincamycin is a derivative of lincomycin (similar to clindamycin) which has been shown to be efficacious against P. falciparum in model systems. Interestingly, there are also reports that it has activity synergistic with the 8-aminoquinoline primaquine in primate models of malaria infection, and so offers a potential as a therapy to treat the liver stages of the disease. Mirincamycin was originally taken into the clinic by Pfizer. We are currently reassessing the IND and preclinical package, with a view to starting studies in normal human volunteers in 2010.

BCX 4945

A series of purine nucleoside phosphorylase inhibitors, known as immucillins, have been discovered in collaboration with Dr Vern Schramm at the Albert Einstein College of Medicine, USA. These inhibitors are based on transition state calculations and high-resolution three-dimensional structures obtained by X-ray crystallography. The molecules were originally developed with a view to modulating T-cell function.

In the current project, original immunology and oncology work done on a series of compounds is being investigated to find out if there are any molecules that show good efficacy against the malaria parasite, and that also have sufficient selectivity for a good safety profile in humans. Currently, the most advanced compound is BCX 4945, which is now in preclinical evaluation. Other, earlier-stage compounds are also being examined.
**Dihydroorotate dehydrogenase (DHODH)**

*P. falciparum* has an absolute requirement for the enzyme DHODH since, unlike most other organisms, it is unable to salvage pyrimidines. As such, DHODH represents a very exciting starting point for drug discovery.

A number of different chemical series have been identified, based on high throughput screening (HTS), and early ‘Hits-to-Leads’ medicinal chemistry has been carried out on these. Several compounds have shown very interesting activity in in vivo models of parasite infection.

Towards the end of 2008, the project team was able to obtain a high resolution three-dimensional structure of the parasite enzyme with one of the inhibitors docked on. This was a major achievement, meaning that the team can now map out the precise interactions needed for a potent molecule, as well as obtain a range of different chemical classes capable of inhibiting the enzyme. We hope that in 2009 we will be able to make significant progress towards selecting a preclinical development candidate.

**Novel macrolides**

The macrolide azithromycin, an antibacterial compound, has been used clinically to treat malaria. As a monotherapy it is slow acting and requires a high dose; it has therefore been partnered with 4-aminoquinolines in clinical development.

We carried out a project in macrolide drug discovery with the GSK Centre of Excellence in Zagreb, Croatia and GSK Diseases of the Developing World centres in Spain, to (1) examine the large collection of macrolides that have been synthesized in Zagreb, and (2) see if a more potent macrolide, with specific action against *P. falciparum*, existed. Unfortunately, although several interesting compounds were identified, none was significantly better than azithromycin across a wide range of assays. As a result the project was discontinued at the end of 2008.

**Ozonides: Next-generation synthetic peroxides**

Our ongoing work to discover synthetic peroxides is based on two premises:

- Synthetic peroxides produced by bulk chemical synthesis can be produced on a large scale, and would be cheaper than using the natural product.
- By extending the half-life of the molecules, it may be possible to find a molecule that can act as part of a single-dose cure.

To date, OZ 277 and OZ 439 (page 30), have been taken up to clinical development. The project team is using detailed pharmacokinetic and pharmacodynamic characterizations to identify new molecules with improved characteristics beyond the current therapies. As with all follow-on programmes, we hope to have as diverse a range of chemistries as possible – in the event that existing programmes come across unexpected toxicological findings.

**Dihydrofolate reductase (DHFR)**

Drugs which inhibit the folate pathway have been widely used for the treatment of *P. falciparum* malaria, but their efficacy is declining due to the emergence of drug resistance. Resistance develops through mutations in the DHFR enzyme. This project has designed and synthesized inhibitors of wild-type and resistant DHFR enzymes, using the three-dimensional structure of DHFR and the knowledge of resistance mechanisms.

By optimizing the compounds for their ability to alter the parasite (resistant) enzyme and not that of the human host, we aim to be able to provide safe and effective compounds that can enter preclinical development over the next 12 months.

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* The project described is supported by Grant Number U01AI075594 from the National Institute of Allergy and Infectious Diseases (NIAID). The content is solely the responsibility of the authors and does not necessarily represent the official views of NIAID or the National Institutes of Health.
**TDR/Pharmacopoeia screening hits**

This project commenced in 2007, and involves compounds discovered through the TDR (UNICEF, UNDP, World Bank, WHO Special Programme for Research and Training in Tropical Disease) programme being optimized by chemists at Pharmacopoeia. Compounds produced through this collaboration are being tested for their activity against *P. falciparum* in the laboratory of Professor Wes Voorhis at the University of Washington, USA. Four different chemical series were worked on in 2008 with interesting activities against the parasite in cell-based assay systems.

**Queensland Natural Products**

This project is based around two resources available at the Eskitis Institute in Queensland, Australia:

- Their natural products collection, assembled from a mixture of Australian and external sources.
- Newly-developed technology for HTS which allows assays to be conducted on the growth and survival of parasites in red blood cells. A unique approach to image processing allows these assays to be quantified without use of radioactivity, making analysis safer.

The availability of high content screening (HCS) technology in a university setting has meant that we have been able to screen compounds from commercial organizations, and rapidly discover if such compounds have activity against whole parasite.

In 2009, the team will use HCS technology to find compounds that have activity against the gametocyte stages of *P. falciparum*. This process, which will broaden understanding of the activity of molecules in our portfolio, is a key part of our eradication strategy.

Given the risks inherent in early-stage discovery, the Mini-portfolio concept was developed by MMV as a way of ensuring that projects could be adequately resourced, and had the built-in flexibility to enable resources to be quickly moved from one project to another.

In this model, the medicinal chemistry is managed by a pharmaceutical or biotechnology company and the Mini-portfolio pipeline is fed with a mixture of projects, such as:

- New targets coming from academic collaborators.
- The results of phenotypic screens.

In all cases, we were able to do live/dead high content screens to identify thousands of compounds with sub-micromolar activities against the whole malaria parasite. These constitute an immense treasure trove of new starting points for medicinal chemistry.

In 2007, we had three Mini-portfolio agreements in place: with GSK at its Drugs for the Developing World site in Tres Cantos, Spain; with Novartis Institute for Tropical Diseases in Singapore (and through it, links to the Genome Foundation of Novartis in San Diego and to other collaborators); and with Genzyme, together with the Broad Research Institute in Boston, USA.

Our partners bring with them drug discovery expertise, and many contributions both in-kind and financial. For 2008, we are happy to be able to announce a new collaboration with sanofi-aventis, which spans discovery and development. We are in active discussions with companies about how we can continue to grow this important early stage part of our work in the future.

**GlaxoSmithKline**

Over the last few years, MMV has had an active project on the 4-pyridone derivatives; this led to the nomination of GSK 932121 as MMV’s clinical development candidate of 2008. Firstly, a pro-drug* has also been identified and is being profiled for preclinical safety. From the same chemical series, two other compounds have been identified with interesting activities in vitro and in vivo. These later compounds also have very long pharmacokinetic and pharmacodynamic half-lives.

The second major project at Tres Cantos has been identification of inhibitors of the cysteine proteases or falcipains – a collaboration with Professor Phillip Rosenthal at the University of California. Compounds have been designed which are extremely potent against parasitic enzymes and show in vivo activity in cell models, but so far, because of the overall reactivity of the compounds, we have not been able to progress to clinical development. The project is focusing on a few remaining approaches.

Third, there has been some work on the fatty acid biosynthesis pathway. This work was initially given a lower priority because of the difficulty in correlating activities on target and in whole-cell assays. However, the recent interesting discovery that this

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* A pro-drug is a precursor of a drug that must undergo chemical conversion by metabolic processes in the body before it becomes an active drug.
pathway has a key role to play in the liver stages of the disease has led to a re-evaluation of the series.

New projects are coming in from the whole-cell screening assay. In 2007, a HCS assay was put in place to study the effect of the entire GSK compound library on the growth and death of P. falciparum. One-and-a-half million compounds have been tested so far, with initial results indicating that some 10,000 compounds show interesting activity (at around 1 micromolar concentrations). These are being retested and clustered with a view to starting a full medicinal chemistry programme over the summer of 2009.

**Novartis**

This portfolio started in earnest in 2007, with a total of 10 different projects – ranging from early-stage research into identifying new targets for liver stages of P. vivax infection, through to optimization of externally identified compounds.

The HCS approach tested over 2 million compounds, and resulted in a collection of some 6,000 confirmed structures that are now being assembled as a ‘malaria toolbox’. This will become a resource that can be used to screen any molecular target through less robust assays at the Genomics Institute of the Novartis Research Foundation (GNF) in San Diego. The initial ‘low hanging fruit’ from this screen are compounds that are highly active against the parasite, yet have no activity against any human targets. Some of these compounds have been selected and are the focus of an intensive medicinal chemistry programme. The screening approach, combined with Novartis’ own collection of molecules obtained from Natural Products, has led to the identification of several families of interesting new molecules, one of which is currently being progressed in the lead optimization stage.

Collaborations with Dominique Mazier in Paris, France and Clemens Kochen in Rijkswijk, Netherlands are looking at the development of hypnozoites in a *P. cynomolgi* model, using fluorescently tagged parasites. These results look particularly exciting since they offer a hint that a high content cell-based assay for hypnozoite biology could become available in the next couple of years. This would be a major breakthrough as the only assay currently available has to be carried out in primates or in patients.

**Broad Institute and Genzyme**

This Mini-portfolio commenced in the second half of 2007, and is based on a collaboration between the Genzyme Corporation and the research groups of Professors Dyann Wirth and Jon Clardy at the Broad Institute of the Massachusetts Institute of Technology (MIT) and Harvard. There have been three major approaches to date:

- Screening of the Broad Institute’s compound collection (which also includes compounds from the Genzyme library) against whole parasite assays. The first molecule to come from this screening led to a lead optimisation programme around aminooindoles.

- The work of Professor Jon Clardy’s group will identify natural products with interesting activities, and use these to discover new molecular targets. This work led to the identification of Hsp-90 as a key target for *P. falciparum*. A screen is being set up to explore this target, and also analyse the properties of existing compounds directed against heat shock proteins (HSP).

- Two other projects have been set up around targets that were already being worked on in the Harvard laboratory - DHODH and HDAC (histone deacetylase). New targets for the collaboration will also come from partnerships between Genzyme and target discovery groups in disease-endemic countries. In 2008, Genzyme signed a landmark agreement with India’s International Centre for Genetic Engineering and Biotechnology (ICGEB) to facilitate the development of new assays based on targets which have been discovered by India’s malaria research groups.

Partnership is also a key element in lead optimization phase chemistry: Genzyme has established key partnerships with Chem Partners, China (in 2007), and with Alvinus, in Bangalore, India (in 2008). These collaborations with chemistry partners help to form a strong foundation for MMV’s discovery work.

**sanofi-aventis**

In the autumn of 2008, MMV signed a memorandum of understanding with sanofi-aventis that covered three areas:

- Classical discovery work, including the support of early-stage molecule testing, and a new screening strategy based on an orthology approach. In the history of the various companies that make up sanofi-aventis, over 1,000 human targets have been screened. Targets that have an ortholog in Plasmodium are selected, and a collection of compounds built up from positives against the human target, as well as structurally related negative compounds. These can then be screened in the whole parasite assay for new target-related starting points.

- We are planning to cooperate by advising on the clinical development plans for three molecules currently in clinical development: ferroquine (a novel 4-aminoquinoline) in Phase II for uncomplicated malaria; SAR 97276, a choline uptake antagonist for severe malaria; and trioxaquone, a fusion amodiaquine/trioxane which is in preclinical development.

- MMV, Drugs for Neglected Diseases initiative (DNDi) and sanofi-aventis are collaborating on a drug efficacy pilot implementation study for Coarsucam™ (amodiaquine/artsunate), which recently obtained prequalification status from the WHO. The idea is to develop a standard implementation trial design that can be used for all of the fixed-dose ACTs currently in development.

* HSPs are a group of proteins which are produced in response to heat or shock.

* An orthology is a gene in two or more species that has evolved from a common ancestor.
NEW CONSORTIA SUPPORTING THE ERADICATION AGENDA

The call for the eradication of malaria announced in November 2007 has been carefully studied for implications for our research strategy. Three areas were identified as priority for discovery:

- Investment in methods to determine resistance to artemisinin and understand its molecular basis.
- Identification of high content assays that would enable us to either predict anti-hypnozoite activity or to measure it in a cell assay.
- Automation and validation of methods to look for compounds with anti-gametocyte activity which will act as transmission cycle-blocking agents. At this stage, it is too early to say whether a pure transmission cycle-blocking molecule would be desirable. Nevertheless, we can ensure that this activity is selected for as one of the factors in all our medicinal chemistry screening cascades.

Artemisinin Resistance Network

One of the long-term questions for any malaria portfolio is the exposure to resistance. So far, there have been reports of patients with increased parasite clearance times when treated with artemisinin. Fortunately, to date none of these reports have been associated with the isolation of a parasite with decreased sensitivity to artemisinin in vitro. If we assume that it is only a matter of time before such a strain emerges, then one question to ask is: Would such a strain show resistance only to artemisinin, or would the resistance mechanism be common to all molecules containing a peroxide bridge?

Liver-stage assays

Programmes that are currently in the discovery phase would be expected to produce new medicines which would be ready for registration in the early 2020s. We anticipate that by this date the overall global burden of *P. falciparum* malaria would have diminished considerably. It is possible that by this stage the reservoir of *P. vivax* malaria will become a much more significant health question. The major difference between the two species is the hypnozoite, or dormant liver stage of *P. vivax*. To date, only one class of compounds, 8-aminoquinolines, is clinically active against this stage.

The search for new medicines is hampered by the fact that no cellular model exists in humans, and that the only reliable model is in primates. With the Novartis Mini-portfolio, we are working on developing an in vitro assay for hypnozoites – as discussed above. In addition, we are working with two groups on the sporozoite* infection model. Although the processes associated with these models are most likely different from the ones that lead to the production of the dormant form of the parasite, there may also be similarities; we believe that some clues on how to handle the hypnozoites may come from these studies.

Gametocyte assays

The role of gametocyte-killing activity in the next generation of antimalarials is going to be very important. We have, therefore, decided to set up high content assays to screen for activity against gametocytes. In the future, all of our molecules will be tested for this activity (a process we call building up the ‘life cycle fingerprint’). Although anti-gametocyte activity is important, it is more important to be able to select those compound series, from the outset, that have dual activity against both erythrocyte (red blood cell) and gametocyte stages.

We will extend this work to medium-throughput assays of the insect stages of the *Plasmodium* lifecycle, as part of our overall characterization package for new molecules. We plan to start screening compounds using these assays in 2009.
Coartem® Dispersible

Every 30 seconds a child dies from malaria. Coartem Dispersible was developed to address the specific treatment needs of millions of children worldwide suffering from this life-threatening disease.

Coartem Dispersible, now approved by Swissmedic and prequalified by WHO, is a sweetened, quick-dispersing formulation that eases administration and promotes effective malaria treatment. Results of studies are encouraging, with a recent study in The Lancet showing that Coartem Dispersible provided the same high efficacy rates and tolerability as Coartem® tablets.

We believe that Coartem Dispersible, the first ACT developed specifically for children, will have a major impact on the lives of over 45 million children worldwide.
Children find the cherry-flavoured, sweet-tasting Coartem® Dispersible easy to swallow once it is dispersed in a little water.

Coartem Dispersible contains the same amounts of artemether and lumefantrine as the existing commercial form of Coartem, the leading ACT in Africa, and is the first dispersible fixed-dose ACT developed specifically for children, to ICH standards.

Dr. Daniel Vasella, Chairman and CEO of Novartis announced: “I am very pleased that we can provide a real innovation, Coartem Dispersible, to help ensure that children with malaria receive the effective treatment. This new dispersible tablet can help improve treatment compliance and potentially save many of the more than 700,000 children under five who die each year from malaria.”

Like Coartem tablets, Coartem Dispersible will be provided to the public sector without profit, to benefit those people most in need in the developing world.

In addition to Swissmedic, Coartem Dispersible has been approved by regulatory authorities in several countries in Africa. These include Benin, Burkina Faso, Democratic Republic of Congo, Gabon, Ghana, Guinea, Côte d’Ivoire, Kenya, Madagascar, Mauritania, Niger, Nigeria, Senegal and Togo.

A randomized, investigator-blinded, multi-centre, parallel-group Phase III study to compare efficacy, safety and tolerability of Coartem Dispersible tablets with Coartem crushed tablets in the treatment of acute uncomplicated falciparum malaria in infants and children. A total of 899 children were included. The study has recently been published in *The Lancet* and demonstrated that Coartem Dispersible tablets provides a high cure rate of 97.8%, comparable to that of Coartem tablets (98.5%). Investigators also reported that Coartem Dispersible had a good safety profile. Dr. Salim Abdulla, the study’s lead investigator confirmed that this new dispersible tablet can help improve treatment compliance and potentially save many of the more than 700,000 children under five who die each year from malaria.

THE DEVELOPMENT TEAM

Novartis project team:
Marc Cousin, Caterina Capaccioli, Nadia ElMasry, Alexandra Glausch, Heiner Grauringer, Nilli Kuhnen, Gilbert LeFebvre, Anne-Claire Marais, Isabelle Meyer, Nathan Muline, Obiyo Nwaiwu, Hans Riefkeld, Daniel Stein, Margaret Weaver

MMV project team:
David Ubben, Stephan DuParc

Institutions and clinical team:
Ifakara Health Institute, Dar es Salaam, Tanzania (S Abdulla MD, J Lyimo MD); Malaria Research and Training Centre, University of Bamako, Bamako, Mali (I Sagara MD, H Maiga MD); Kenya Medical Research Institute, Kisumu, Kenya (S Borrmann MD, P Sasi MD); Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium (U D’Alessandro MD); Centre de Recherche Entomologique de Cotonou, Cotonou, Benin (A Nahum MD); Barcelona Centre for International Health Research (CRESIB), Hospital Clinic, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Spain and Manhiça Health Research Centre (CISM), Manhiça, Mozambique (R Gonzalez MD, Q Bassat MD); Malaria Branch, Centers for Disease Control and Prevention, Kenya Medical Research Institute, Kisumu, Kenya (H Hamel MD); Walter Reed Project, Kenya Medical Research Institute, Kisumu, Kenya (B Ogutu MD, L Otieno MD); Karolinska University Hospital, Stockholm, Sweden and Zarzibar Malaria Research Unit of the Karolinska Institutet, Zarzibar, Tanzania (A Mårtensson MD, A Bjorkman MD); Kilbargskas Hospital, Kaahvinholm, Sweden (A Mårtensson MD); Kenya Medical Research Institute, Kisumu, Kenya (B Juma MD); Swiss Tropical Institute, Basel, Switzerland (H P Beck PhD); and Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania (Z Premji MD).

Chris Hentschel, President and CEO of MMV stated: “The launch of Coartem Dispersible is an important milestone in the fight against malaria and marks the culmination of several years of successful collaboration with Novartis. As malaria is essentially a pediatric disease, we are certain this child-friendly formulation will contribute significantly to a reduction in child mortality in Africa, and give children back their future.”

BEHIND THE SCENES AT MMV

Expert Scientific Advisory Committee (ESAC)
Salim Abdool Karim, Director, Aglanoko Branch, Ekapra Health Institute, Tanzania
Pedro Alonso Head and Professor, Barcelona Centre for International Health Research (CrebiE), Spain
Simon Campbell Chemist, former Senior Vice-President, Worldwide Discovery and Medica
Bill Curnow, Dean, Monash University, Melbourne, Australia
Kelly Chibale US Fulbright Senior Research Scholar, University of Pennsylvania, USA
Christine Clayton Lecturer, Centre for Molecular Biology, Heidelberg, Germany
Simon Croft Head of Department, Infectious & Tropical Diseases, London School of Hygiene and Tropical Medicine (LSHTM), UK
Ogida Dumbro Director, Malaria Research and Training Centre, Bamako, Mali
Brian Greenwood Marion Professor of Clinical Tropical Medicine, LSHTM, UK
Kip Day Chairman and Member of the Department of Chemical Biology and Therapeutics, St Jude Children’s Research Hospital, USA
Alan Hudson Managing Director, Pharmaco-
Charlott Labrie President, Regulatory Affairs, Eradication of Malaria in Madagascar (EMMA), France
Trevor Laird Managing Director/Owner, Scientific Update, UK
Michael Miekings Capacity Building Manager, EDCTP Secretariat, Cape Town, South Africa
Mauroz Mariani General Manager, Merck Serono Research, Italy
David Mathews Ffounder, Agouron Pharma-
David McGibney Pharmaceutical Research and Development Expert, UK; ESAC Chairmen Development
Wilbur Milhous Associate Dean, Research, College of Public Health, University of South Florida, USA
Francois Nosten Director, Shoklo Malaria Research Unit, Thailand
Bernhardt Ogutu Principal Research Officer, Kenya Medical Research Institute Clinical Trials Unit, Kenya
Mag Phillips Professor, University of Texas Southwestern Medical Center, USA
Carol Sibley Professor, Department of Genomic Science, University of Washington, USA

Access & Delivery Advisory Committee (ADAC)
Joseph Amovuza; Retired Pharmacists, Barin Gombo, Head of Pharmacy, Ghana, Head of Pharmacy, Ghana, Head of Pharmacy, Ghana
Awa Marie Coll-Bekk Executive Director, Roll Back Malaria Partnership, Switzerland; Chairman, ADAC
Issa Diop Technical Advisor to the Ministry of Health, Senegal
Paul Lahiri Executive Director, PhaID Pharmacovigilance Program, USA
P A Narayan, Entrepreneur, Pharmaceutical Consultant, India
Naavae Siplanyamba Malaria Specialist (Malaria Scale up), UNICEF HQ, USA
Francisco Borgaon Head, Neonatal, Maternal and Child Health Partnership, Switzerland
Marcel Tanner Director, Swiss Tropical Institute, Switzerland
Geoff Targett Director, Global Malaria Partnership, LSHTM, UK
Prashant Yadav Professor, Supply-Chain Management, MIT-Zaragoza International Logistics Programme, Spain
Hashim Yusuf Deputy Director, National Agency for Food & Drug Administration and Control (NAFDAC), Nigeria

MMV Team 2009
Nada Arawi: Legal Assistant
Jaya Banerji: Head, Communications
Jan Barth: Director, Drug Discovery & Technology
Isabelle Birghei: Associate Director, Clinical Science
Jeremy Burrows: Associate Director, Drug Discovery
Renata Coghlan: Associate Director, Global Access
Diana Crichton: Executive Vice President, Operations
Maud Couturier: Scientific Coordinator
Christine Daquet: Assistant Manager, Finance & Budget
Matthew Doherty: Financial Assistant
Stephan Durand: Medical Director
Alejandro Estrada: Office Assistant
Pascal Fantauzi: Associate Director, Drug Discovery
Sylvie Fayette: Director, Drug Discovery
Penny General: Director, Global Access
Roberto Hanania: Contracts Officer
Chris Herrschel: President and Chief Executive Officer
George Jagoe: Executive Vice President, Global Access
Tony Kam: Executive Vice President, Corporate Development
Elizabeth Kemen: Researcher and Administrative Assistant
Elin Kim: Personal Assistant to President & CEO, Website Administrator
Didier Leroy: Associate Director, Drug Discovery
Julie Lotharius: Associate Director, Translational Medicine
Maud Luyang: Operations and Communications Assistant
Jörg Möhrle: Director, Clinical Development
Patrick Nuf: Chief Business Officer
Claude Oceay: Associate Director, Clinical Development
Sophie Patel: Finance Assistant
Ole Peter-Petersen: Human Resources Generalist
Elizabeth Poll: Editor and Publications Officer
Peter Potter-League: Chief Financial Officer
Rana Rossignol: Personal Assistant to the CEO
Samuel Stamo: Finance Officer
David Urban: Director, Clinical Development
Timothy Watts: Chief Scientific Officer
FINANCIAL VIEW – 2008

Financial year to 31 December 2008

Summary

Medicines for Malaria Venture (MMV) receives funding and support from government agencies, private foundations, international organizations, corporations, corporate foundations, and private individuals. These funds are used to finance the MMV portfolio of research and development (R&D) projects to provide new, effective and affordable medicines for the treatment and prevention of malaria. They also support specific, targeted access and delivery (A&D) interventions to facilitate access to MMV products by vulnerable populations in malaria-endemic countries.

As a not-for-profit Swiss foundation 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.
Remarkably, in contrast to the somewhat gloomy overall economic environment, for MMV 2008 was a very successful financial year which ensured sustained progress of the full R&D portfolio. This ninth year of operations saw the final registration of our first drug, two projects in late-stage Phase III clinical trials, three mini-Portfolios and multiple pre-clinical and discovery phase collaborations – 50 projects in all. Malaria drug R&D expenditure increased (by 11%) as did overall expenditure, which reached USD 55.8 million compared to USD 47.9 million in 2007. Also, rather encouragingly, the expenditure on recently implemented activities to facilitate AID of MMV’s new products more than doubled, from USD 1.6 million in 2007 to USD 3.4 million in 2008.

Continued efforts to secure supplementary funding brought significant new commitments from the Spanish government and USAID. Further proposals submitted to other donors are still under consideration. Moreover, MMV is now increasing its capacity in the Corporate Development and Advocacy area.

The amount of funds pledged to MMV since its foundation increased in 2008 by US$ 12 million – from US$ 318 million to over US$ 330 million to 2013. The considerable 2008 cash surplus produced (Operations Reserve) will be carried over to fund activities during 2009, which is normal MMV practice.

MMV’s financial infrastructure continues to evolve to meet the growing needs of the organization. Three new interconnected financial risk management projects were fully implemented and validated in 2008 – an internal control system, a new financial reporting system, and an integrated electronic transfer system – to further enhance financial capacity and transparency. In addition, two new members joined the team.

International Financial Reporting Standards (IFRS)
The transition to International Financial Reporting Standards (IFRS) brought the benefits of increased transparency and disclosure. MMV Financial Statements 2007 were the first to be issued under these standards, and the organization’s operating procedures are constantly updated in line with evolving requirements. Now mandatory for European listed companies, IFRS offers a real drive to greater disclosure, transparency and international comparison of financial figures.

Financial year ahead to December 2009

MMV operates in a complex multi-currency environment. The bulk of donations are received in US dollars, although other currencies are sometimes involved. Out-flows for projects are mostly in USD, the standard currency used in the various agreements signed with project partners. Many operational expenses, however, are in Swiss Francs (CHF). The resulting exposure or exchange risk is hedged according to the budget in January and at regular intervals over the year, to provide a nominal fixed result so as to provide a degree of financial security for the foundation. The foundation capital remained unchanged at 31 December 2008.

Management & Administration
Management and administration costs increased during 2008 as MMV’s staff headcount went up significantly from 23 to 33 with much additional work undertaken on building capacity for the future. Consequently, the ratio of management & administration expenditure to overall spending increased to 10.6% as compared with 9.7% in 2007, 6.8% in 2006 and 11.1% in 2005.

Funding
In addition to previous pledges, MMV received the following new pledges in 2008, as fundraising continues to progress:

<table>
<thead>
<tr>
<th>Donor (new pledges)</th>
<th>Currency</th>
<th>Amount</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spanish Government</td>
<td>EUR</td>
<td>3 million</td>
<td>2008</td>
</tr>
<tr>
<td>USAID</td>
<td>USD</td>
<td>8 million</td>
<td>4 years</td>
</tr>
</tbody>
</table>

MMV is grateful for these and previous commitments from its many donors.

Financial View


Research & Development Expenditure

Foundations Capital
By 31 December 2003, the stipulated foundation capital of USD 4,000,000 was fully subscribed (in a Swiss foundation it is a legal requirement that the foundation capital should be constituted without delay so as to provide a degree of financial security for the foundation). The foundation capital remained unchanged at 31 December 2008.

Donations & Pledges 2008
Cash received at bank amounted to USD 47,363,329, with USD 3,629,806 from the Dutch government and USD 176,039 recognized from the previous year, USD 178,285 from NIH deferred to 2009 and USD 2,780,200 current 2008 income from Irish Aid to be received in 2009.

In addition to previous pledges, MMV received the following new pledges in 2008, as fundraising continues to progress:

<table>
<thead>
<tr>
<th>Donor (new pledges)</th>
<th>Currency</th>
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<td>4 years</td>
</tr>
</tbody>
</table>

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Project-related R&D Expenditure

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management &amp; Administration</td>
<td>10.6%</td>
</tr>
<tr>
<td>Governance &amp; Stakeholders</td>
<td>0.8%</td>
</tr>
<tr>
<td>Access &amp; Delivery</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

Research & Development Expenditure
The scientific project-related expenditure increased to USD 55.8 million compared to USD 47.9 million in 2007. Also, rather encouragingly, the expenditure on recently implemented activities to facilitate AID of MMV’s new products more than doubled, from USD 1.6 million in 2007 to USD 3.4 million in 2008.

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Financial year ahead to December 2009

MMV operates in a complex multi-currency environment. The bulk of donations are received in US dollars, although other currencies are sometimes involved. Out-flows for projects are mostly in USD, the standard currency used in the various agreements signed with project partners. Many operational expenses, however, are in Swiss Francs (CHF). The resulting exposure or exchange risk is hedged according to the budget in January and at regular intervals over the year, to provide a nominal fixed average US$/CHF budget rate for the period. The accounts are kept in US dollars.

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 more effectively manage the growing R&D portfolio. It also provides a base analysis for fundraising activities aimed at financing the portfolio in line with the projections of the MMV Business Plan 2008-2012.

Given the current financial environment and market conditions, it is evident that the portfolio, cash flow and new potential fundraising opportunities have to be managed even more dynamically.
Focus on Sustainability: R&D and Access & Delivery

In 2008, MMV continued to prepare scale-up and launch activities to ensure market access to medicines emerging from its pipeline. These activities will enable a “downstream” extension of the public-private partnership model underpinning MMV’s fundamental goal – to achieve major health impact from its products. Moreover, in the new context of malaria elimination/eradication, a second and critical series of investments are now urgently needed to spur on R&D for the next generation of antimalarial drugs designed specifically to meet that goal.

Although fundraising remains successful, given the significant additional funds again sourced in 2008, major fundraising efforts will be required in 2009 and beyond, as MMV strives to meet the projected requirements of its new Business Plan 2008–2012.

Financial Modelling

To date, of the USD 330 million received pledged to 2013 by 14 donors, MMV has spent USD 255 million over 9 years building the largest-ever pipeline of antimalarial drug projects. Financial modelling (figure 3) suggests that, in spite of the increase in funding for MMV in 2008, future R&D and Access activities will remain substantially under-funded. Current forecasts for future MMV overall spending are USD 70–75 million in 2009, and thereafter an average of USD 80–100 million annually, that represents a mixture of R&D, product launch and Access-related spending.

Since its foundation, MMV has been granted multi-year pledges of funding for its R&D portfolio, notably from the Bill & Melinda Gates Foundation, the UK Department for International Development, the Swiss Agency for Development and Cooperation, Irish Aid, the Netherlands Ministry of Foreign Affairs, the Rockefeller Foundation, USAID, National Institutes of Health (NIH), ExxonMobil Foundation, BHP Billiton and the Wellcome Trust. These statements and all forward-looking financial figures should be considered as management’s best estimates based on information available at the time of printing (April 2009).

Financial Tables

The financial tables and notes that follow are extracted from the International Financial Reporting Standards compliant accounts. We are one of the first product development public-private partnerships (PDPs) and among the first not-for-profit organizations to report using these widely accepted international standards.
### MMV STATEMENT OF INCOME & EXPENDITURE FOR THE YEAR ENDED 31 DECEMBER 2008

#### INCOME

<table>
<thead>
<tr>
<th></th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DONATION REVENUES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private Foundations &amp; Individual Donors</td>
<td>33 754 850</td>
<td>61 021 228</td>
</tr>
<tr>
<td>UN Agencies</td>
<td>710 000</td>
<td>750 000</td>
</tr>
<tr>
<td>Government Agencies</td>
<td>18 556 438</td>
<td>12 888 246</td>
</tr>
<tr>
<td>Corporations &amp; Corporate Foundations</td>
<td>750 000</td>
<td>750 000</td>
</tr>
<tr>
<td><strong>TOTAL DONATIONS RECEIVED</strong></td>
<td>53 771 088</td>
<td>75 405 474</td>
</tr>
</tbody>
</table>

#### OTHER INCOME

<table>
<thead>
<tr>
<th></th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial Income, net</td>
<td>1 195 054</td>
<td>1 288 639</td>
</tr>
<tr>
<td>Other</td>
<td>92 415</td>
<td>80 420</td>
</tr>
<tr>
<td><strong>TOTAL OTHER INCOME</strong></td>
<td>1 377 469</td>
<td>1 550 059</td>
</tr>
</tbody>
</table>

**TOTAL INCOME**: 55 148 885 (76 965 362)

#### EXPENDITURE

<table>
<thead>
<tr>
<th></th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESEARCH &amp; DEVELOPMENT EXPENDITURE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Project-related Variable Expenditure</td>
<td>7 458 185</td>
<td>41 291 443</td>
</tr>
<tr>
<td>Expert Scientific Advisory Committee Expenses</td>
<td>410 494</td>
<td>203 238</td>
</tr>
<tr>
<td>TOTAL RESEARCH &amp; DEVELOPMENT EXPENDITURE</td>
<td>46 028 889</td>
<td>41 494 679</td>
</tr>
</tbody>
</table>

#### ACCESS EXPENDITURE

<table>
<thead>
<tr>
<th></th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access-related Variable Expenditure</td>
<td>3 332 916</td>
<td>1 494 991</td>
</tr>
<tr>
<td>Access &amp; Delivery Advisory Committee</td>
<td>55 553</td>
<td>55 229</td>
</tr>
<tr>
<td><strong>TOTAL ACCESS EXPENDITURE</strong></td>
<td>3 388 469</td>
<td>1 550 220</td>
</tr>
</tbody>
</table>

#### FOUNDATION BOARD & STAKEHOLDER EXPENSES

<table>
<thead>
<tr>
<th></th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 442 005</td>
<td>269 544</td>
<td></td>
</tr>
</tbody>
</table>

#### GENERAL AND ADMINISTRATION EXPENSES

<table>
<thead>
<tr>
<th></th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staff-related Benefits – Compensation</td>
<td>3 109 964</td>
<td>2 286 180</td>
</tr>
<tr>
<td>Office and Occupancy</td>
<td>8 512 825</td>
<td>602 063</td>
</tr>
<tr>
<td>Travel Expenses</td>
<td>287 389</td>
<td>203 206</td>
</tr>
<tr>
<td>Fundraising</td>
<td>168 754</td>
<td>132 101</td>
</tr>
<tr>
<td>Professional and Legal Fees</td>
<td>363 579</td>
<td>510 131</td>
</tr>
<tr>
<td>Training, Education and Journals</td>
<td>57 551</td>
<td>153 784</td>
</tr>
<tr>
<td>IF Expenses</td>
<td>365 752</td>
<td>286 420</td>
</tr>
<tr>
<td>Communications</td>
<td>474 094</td>
<td>291 938</td>
</tr>
<tr>
<td>Depreciation</td>
<td>229 147</td>
<td>138 487</td>
</tr>
<tr>
<td>Other</td>
<td>37 167</td>
<td>26 513</td>
</tr>
<tr>
<td><strong>TOTAL GENERAL ADMINISTRATION EXPENSES</strong></td>
<td>5 914 231</td>
<td>4 834 871</td>
</tr>
</tbody>
</table>

**TOTAL EXPENDITURE**: 55 773 594 (47 946 314)

#### NET RESULT

<table>
<thead>
<tr>
<th></th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>824 709</td>
<td>29 019 066</td>
<td></td>
</tr>
</tbody>
</table>

#### ALLOCATIONS

<table>
<thead>
<tr>
<th></th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer from / (to) Operations Reserve</td>
<td>872 581</td>
<td>(18 818 723)</td>
</tr>
<tr>
<td>Transfer from / (to) Donor Restricted Reserve</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Transfer from / (to) Foreign Exchange Reserve</td>
<td>(247 882)</td>
<td>(203 333)</td>
</tr>
<tr>
<td><strong>TOTAL ALLOCATIONS</strong></td>
<td>624 709</td>
<td>(29 019 066)</td>
</tr>
</tbody>
</table>

### MMV STATEMENT OF CASH FLOWS TO 31 DECEMBER 2008

#### EXCESS OF INCOME/(EXPENDITURE) FOR THE YEAR

<table>
<thead>
<tr>
<th></th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Decrease)/Increase in Provisions</td>
<td>5</td>
<td>47 823</td>
</tr>
<tr>
<td>(Decrease) in Non-current Liabilities</td>
<td>6</td>
<td>(17 391)</td>
</tr>
<tr>
<td><strong>Depreciation</strong></td>
<td>4</td>
<td>229 147</td>
</tr>
</tbody>
</table>

**OPERATING RESULT BEFORE WORKING CAPITAL CHANGES**: 490 130 (29 494 468)

#### CASH FLOWS FROM OPERATING ACTIVITY

<table>
<thead>
<tr>
<th></th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Increase) in Donations Receivable</td>
<td>(2 780 200)</td>
<td>0</td>
</tr>
<tr>
<td>Decrease/(Increase) in Project Balance Reimbursements</td>
<td>22 404</td>
<td>(22 404)</td>
</tr>
<tr>
<td>Decrease/(Increase) in Accounts Receivable</td>
<td>200 015</td>
<td>(122 243)</td>
</tr>
<tr>
<td>Decrease in Recoverable Withholding Tax</td>
<td>21 859</td>
<td>86 400</td>
</tr>
<tr>
<td>(Increase)/Decrease in Project-related Prepaid Expenses</td>
<td>(54 456)</td>
<td>(153 637)</td>
</tr>
<tr>
<td>(Decrease)/Increase in Accrued R&amp;D Commitments</td>
<td>2 848 932</td>
<td>(2 596 466)</td>
</tr>
<tr>
<td>Increase in Accrued A&amp;D Commitments</td>
<td>459 565</td>
<td>141 382</td>
</tr>
<tr>
<td>(Decrease)/(Increase) in Deferred Income</td>
<td>(3 627 567)</td>
<td>(113 766)</td>
</tr>
<tr>
<td>(Decrease)/Increase in Other Creditors</td>
<td>85 764</td>
<td>(57 473)</td>
</tr>
<tr>
<td>Increase in Accrued Expenses</td>
<td>(40 656)</td>
<td>177 525</td>
</tr>
<tr>
<td><strong>TOTAL CASH FLOW RESULTING FROM OPERATING ACTIVITY</strong></td>
<td>(3 954 384)</td>
<td>(3 680 882)</td>
</tr>
</tbody>
</table>

#### CASH FLOWS FROM INVESTMENT ACTIVITY

<table>
<thead>
<tr>
<th></th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Increase) in Guarantees</td>
<td>(32 553)</td>
<td>(6 089)</td>
</tr>
<tr>
<td>(Increase) in Fixtures and Installations</td>
<td>4</td>
<td>(169 307)</td>
</tr>
<tr>
<td>(Increase) in Office Furniture</td>
<td>4</td>
<td>(37 054)</td>
</tr>
<tr>
<td>(Increase) in Computers and Equipment</td>
<td>4</td>
<td>(96 469)</td>
</tr>
<tr>
<td><strong>TOTAL CASH FLOW RESULTING FROM INVESTMENT ACTIVITY</strong></td>
<td>(395 003)</td>
<td>(133 139)</td>
</tr>
</tbody>
</table>

#### NET VARIATION OF CASH AND CASH EQUIVALENTS

<table>
<thead>
<tr>
<th></th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3 849 517)</td>
<td>26 700 647</td>
<td></td>
</tr>
</tbody>
</table>

**Cash and cash equivalents at beginning of year** | 46 526 744 | 39 826 097 |
**Cash and cash equivalents at end of year** | 42 677 227 | 46 526 744 |

### MMV STATEMENT OF RECOGNIZED INCOME AND EXPENDITURE

#### Capital Fund (USD)

<table>
<thead>
<tr>
<th></th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance at 1 January 2007</td>
<td>4 000 000</td>
<td>5 207 867</td>
</tr>
<tr>
<td>Allocation of result for the year</td>
<td>0</td>
<td>28 818 733</td>
</tr>
<tr>
<td>Effect of initial recognition of post-retirement obligation</td>
<td>(565 886)</td>
<td>(565 886)</td>
</tr>
<tr>
<td><strong>Balance at 31 December 2007</strong></td>
<td>4 000 000</td>
<td>33 459 712</td>
</tr>
<tr>
<td>Allocation of result for the year</td>
<td>0</td>
<td>(872 581)</td>
</tr>
<tr>
<td>Effect of initial recognition of post-retirement obligation</td>
<td>0</td>
<td>247 883</td>
</tr>
<tr>
<td><strong>BALANCE AT 31 DECEMBER 2008</strong></td>
<td>4 000 000</td>
<td>32 587 121</td>
</tr>
</tbody>
</table>

#### Total Capital and Reserves (USD)

<table>
<thead>
<tr>
<th></th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>824 709</td>
<td>29 019 066</td>
<td></td>
</tr>
</tbody>
</table>
NOTES TO THE FINANCIAL STATEMENTS AS OF 31 DECEMBER 2008

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 6 senior managers (2007: 3).

With its head-office in Geneva, MMV’s aim is to bring public and private sector partners together to fund, 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 financial statements were approved for issue by the MMV Board on 30 March 2009.

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

Statement of compliance
The financial statements have been prepared on the historical cost basis, except where a standard requires a different measurement basis. They are presented in US dollars, since the majority of MMV’s activities are conducted in this currency.

Basis of preparation
The financial statements are presented in US dollars, since the majority of MMV’s activities are conducted in this currency. They are prepared on the historical cost basis.

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

The preparation of financial statements in conformity with IFRS 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 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 IFRSs that have significant effects on the financial statements and estimates with a significant risk of material adjustment in the next year are discussed below.

The accounting policies set out below have been applied consistently to all periods presented in these financial statements.

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 balance sheet date are translated to USD at the foreign exchange rate ruling at that date. Foreign exchange differences arising on translation are recognized in the statement of income and expenditure. 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:

<table>
<thead>
<tr>
<th>Year</th>
<th>CHF</th>
<th>USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>1 CHF</td>
<td>0.9395</td>
</tr>
<tr>
<td></td>
<td>1 EUR</td>
<td>1.3901</td>
</tr>
<tr>
<td></td>
<td>1 GBP</td>
<td>1.4377</td>
</tr>
</tbody>
</table>

2007

<table>
<thead>
<tr>
<th>Year</th>
<th>CHF</th>
<th>USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>1 CHF</td>
<td>0.8833</td>
</tr>
<tr>
<td></td>
<td>1 EUR</td>
<td>1.4621</td>
</tr>
<tr>
<td></td>
<td>1 GBP</td>
<td>1.9907</td>
</tr>
</tbody>
</table>

Cash and cash equivalents
Cash and cash equivalents comprise cash balances and short-term money market investments 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 statement of income and expenditure 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
Office fixtures and installations – 3 years
Computers and equipment – 3 years

Impairment
The carrying amounts of MMV’s assets are reviewed at each balance sheet 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 statement of income and expenditure whenever the recoverable amount of an asset exceeds its recoverable amount.

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

Employee benefits
MMV maintains a retirement plan for its employees. This plan is considered as a defined benefit plan under IAS 19. The valuation is carried out annually by independent actuaries based on the projected unit credit method. Pension costs primarily represent the increase in the actuarial present value of the obligation for projected pension benefits based on employee service during the year and the interest on this obligation in respect of employee service in previous years, net of the expected return on plan assets.

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. Under exceptional circumstances, Founders Capital must be used to maintain the viability of the organization, for 6 to 9 months, until other funding sources can be found.

Revenue recognition
An exceptional grant is recognized as revenue in the statement of income and expenditure when the grant becomes receivable. Any other grant which has performance or other conditions is recognized in the balance sheet initially as deferred income when there is reasonable assurance that it will be received and that the foundation will comply with the conditions attaching to it, and recognized as revenue when these conditions are satisfied.

A reconciliation between donations received in cash and income recognized in the statement of income and expenditure is shown in note 6.

Operations reserve
Accumulated Operations Reserve represents excess of income 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.

Foreign exchange reserve
Expenditure for operational costs in Geneva is denominated in Swiss Francs. The Foreign Exchange Reserve serves as a segregated fund for use to reduce the impact of future adverse currency fluctuations.

Financial income (expense), net
Financial income (expense), net comprises interest on funds invested, bank charges and foreign exchange gains and losses.

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 grantors.

In the event that a portion of a grant is unspent at the year-end, it is included under current liabilities. Expenses paid before year-end for the following year are recorded as Prepaid R&D Commitments in current assets and as Prepaid in Note 7.

Revenue recognition
MMV has received exemption from income tax from the Geneva cantonal and Swiss federal authorities from the year 2000 for an indeterminate period.

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 program 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 program participants and sponsors.

Research and Development Expenditure – MMV’s research and development expenditure is generally not direct expenditure, but is in the form of grants and contracts with external parties who perform certain tasks at our request. These requests are formalized by cost sharing 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.

New standards and interpretations
A number of new standards, amendments to standards and interpretations have been issued, but are not yet effective for the year ended 31 December 2008, and have not been applied in preparing these financial statements.
3. CASH AND CASH EQUIVALENT

<table>
<thead>
<tr>
<th></th>
<th>At 31 December 2008 (USD)</th>
<th>At 31 December 2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash</td>
<td>974</td>
<td>1 643</td>
</tr>
<tr>
<td>Bank balances</td>
<td>3 908 003</td>
<td>2 869 001</td>
</tr>
<tr>
<td>Money market deposits - with maturity less than three months</td>
<td>38 768 250</td>
<td>43 656 700</td>
</tr>
<tr>
<td><strong>TOTAL CASH AND CASH EQUIVALENTS</strong></td>
<td><strong>42 677 227</strong></td>
<td><strong>48 528 744</strong></td>
</tr>
</tbody>
</table>

The effective rate on money market deposits have moved within the following ranges:

<table>
<thead>
<tr>
<th>Currency</th>
<th>2008 Low %</th>
<th>2008 High %</th>
<th>2007 Low %</th>
<th>2007 High %</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Dollar (USD)</td>
<td>0.71</td>
<td>4.91</td>
<td>4.58</td>
<td>5.31</td>
</tr>
<tr>
<td>Swiss Franc (CHF)</td>
<td>0.58</td>
<td>2.41</td>
<td>1.31</td>
<td>2.46</td>
</tr>
<tr>
<td>British Pound (GBP)</td>
<td>4.95</td>
<td>5.80</td>
<td>5.44</td>
<td>6.12</td>
</tr>
<tr>
<td>Euro (EUR)</td>
<td>2.00</td>
<td>4.72</td>
<td>3.92</td>
<td>4.13</td>
</tr>
</tbody>
</table>

4. FIXED ASSETS

<table>
<thead>
<tr>
<th>Year</th>
<th>Fixtures and Installations (USD)</th>
<th>Office Furniture (USD)</th>
<th>Computers and Equipment (USD)</th>
<th>Total (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COST</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>127 175</td>
<td>187 596</td>
<td>256 252</td>
<td>571 023</td>
</tr>
<tr>
<td>Additions</td>
<td>5 511</td>
<td>17 595</td>
<td>103 944</td>
<td>127 050</td>
</tr>
<tr>
<td>At 31 December 2007</td>
<td>132 686</td>
<td>205 191</td>
<td>360 196</td>
<td>698 073</td>
</tr>
<tr>
<td><strong>ACCUMULATED DEPRECIATION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>67 194</td>
<td>122 408</td>
<td>160 845</td>
<td>350 445</td>
</tr>
<tr>
<td>Charge for the year</td>
<td>34 681</td>
<td>20 960</td>
<td>82 846</td>
<td>138 487</td>
</tr>
<tr>
<td>At 31 December 2007</td>
<td>101 875</td>
<td>143 568</td>
<td>243 489</td>
<td>486 932</td>
</tr>
<tr>
<td><strong>NET BOOK VALUE AT 31 DECEMBER 2007</strong></td>
<td>30 811</td>
<td>61 623</td>
<td>116 707</td>
<td>209 141</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Fixtures and Installations (USD)</th>
<th>Office Furniture (USD)</th>
<th>Computers and Equipment (USD)</th>
<th>Total (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COST</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>132 686</td>
<td>205 191</td>
<td>360 196</td>
<td>698 073</td>
</tr>
<tr>
<td>Additions</td>
<td>168 007</td>
<td>97 054</td>
<td>96 490</td>
<td>362 551</td>
</tr>
<tr>
<td>At 31 December 2008</td>
<td>301 593</td>
<td>302 245</td>
<td>456 686</td>
<td>1 060 524</td>
</tr>
<tr>
<td><strong>ACCUMULATED DEPRECIATION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>101 875</td>
<td>143 568</td>
<td>243 489</td>
<td>486 932</td>
</tr>
<tr>
<td>Charge for the year</td>
<td>85 276</td>
<td>39 236</td>
<td>104 835</td>
<td>229 147</td>
</tr>
<tr>
<td>At 31 December 2008</td>
<td>187 151</td>
<td>182 804</td>
<td>346 124</td>
<td>718 079</td>
</tr>
<tr>
<td><strong>NET BOOK VALUE AT 31 DECEMBER 2008</strong></td>
<td>114 442</td>
<td>119 441</td>
<td>108 562</td>
<td>342 445</td>
</tr>
</tbody>
</table>

5. PROVISIONS

<table>
<thead>
<tr>
<th>Service-related</th>
<th>Unused Vacation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provisions Reserve</td>
<td>Reserve</td>
<td>Provisions Reserve</td>
</tr>
<tr>
<td>(USD)</td>
<td>(USD)</td>
<td>(USD)</td>
</tr>
<tr>
<td>Balance at 1 January 2007</td>
<td>0</td>
<td>160 000</td>
</tr>
<tr>
<td>Use/release 2007</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Allocation for the year</td>
<td>413 384</td>
<td>100 000</td>
</tr>
<tr>
<td>Balance at 31 December 2007</td>
<td>413 384</td>
<td>260 000</td>
</tr>
<tr>
<td>Used during the year</td>
<td>(55 665)</td>
<td>0</td>
</tr>
<tr>
<td>Unused amount released</td>
<td>0</td>
<td>103 488</td>
</tr>
<tr>
<td><strong>BALANCE AT 31 DECEMBER 2008</strong></td>
<td><strong>357 719</strong></td>
<td><strong>363 488</strong></td>
</tr>
</tbody>
</table>

6. DONATIONS*

<table>
<thead>
<tr>
<th>Donor</th>
<th>Cash</th>
<th>Income recognized from previous year (USD)</th>
<th>Income deferred to following year (USD)</th>
<th>Current year income to be received (USD)</th>
<th>Total Income as per I&amp;E account (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bill &amp; Melinda Gates Foundation</td>
<td>30 000 000</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30 000 000</td>
</tr>
<tr>
<td>Welcome Trust</td>
<td>3 743 800</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 743 800</td>
</tr>
<tr>
<td>Swiss Government (DEZA/SDC)</td>
<td>677 988</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>677 988</td>
</tr>
<tr>
<td>UK Government (DFID)</td>
<td>3 789 500</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 789 500</td>
</tr>
<tr>
<td>Dutch Government (NMDC)</td>
<td>-</td>
<td>3 629 806</td>
<td>-</td>
<td>-</td>
<td>3 629 806</td>
</tr>
<tr>
<td>US Government (US$)</td>
<td>1 500 020</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 500 020</td>
</tr>
<tr>
<td>Irish Aid</td>
<td>1 269 300</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 269 300</td>
</tr>
<tr>
<td>Spanish Government</td>
<td>3 849 300</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 849 300</td>
</tr>
<tr>
<td>National Institutes of Health (NIH)</td>
<td>710 000</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>710 000</td>
</tr>
<tr>
<td>World Bank via Global Forum</td>
<td>3 629 806</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 629 806</td>
</tr>
<tr>
<td>ExxonMobil</td>
<td>1 500 020</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 500 020</td>
</tr>
<tr>
<td>Individual donors</td>
<td>10 850</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10 850</td>
</tr>
<tr>
<td><strong>TOTAL RECEIVED</strong></td>
<td><strong>47 363 329</strong></td>
<td><strong>3 805 844</strong></td>
<td><strong>(178 285)</strong></td>
<td><strong>2 780 200</strong></td>
<td><strong>53 771 088</strong></td>
</tr>
</tbody>
</table>

* Summary of donations received or committed during 2008.
### 7. PROJECT-RELATED VARIABLE EXPENDITURE

#### CLINICAL DEVELOPMENT PROJECTS

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>17 488 376</td>
<td>13 036 673</td>
<td>4 461 703</td>
</tr>
<tr>
<td>Coartem® (artemether-lumefantrine) Dispersible Tablets - Approved 1</td>
<td>255 369</td>
<td>255 369</td>
</tr>
<tr>
<td>EDCTP Longitudinal (TB) 2</td>
<td>283 178</td>
<td>283 178</td>
</tr>
<tr>
<td>Pyramax® (pyrnamidine-artesunate) 3</td>
<td>9 464 851</td>
<td>8 798 938</td>
</tr>
<tr>
<td>Eurartesim® (dihydroartemisinin-piperaquine) 4</td>
<td>2 645 988</td>
<td>666 253</td>
</tr>
<tr>
<td>Dapac® (trisopropyl-oxide artesunate) - Discontinued 5</td>
<td>945 703</td>
<td>119</td>
</tr>
<tr>
<td>Artesunate iv (intravenous form) 5</td>
<td>534 359</td>
<td>465 004</td>
</tr>
<tr>
<td>Mefloquine 6</td>
<td>3 911</td>
<td>9 055</td>
</tr>
<tr>
<td>Tafenoquine 7</td>
<td>251 506</td>
<td>0</td>
</tr>
<tr>
<td>GSK 3937956 Serotype 8</td>
<td>2 923 787</td>
<td>2 348 598</td>
</tr>
</tbody>
</table>

#### DISCOVERY PROJECTS

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4 485 701 9</td>
<td>10 000</td>
<td>10 000</td>
</tr>
<tr>
<td>Dihydroorotate Dihydrogenase (DHODH) Inhibitor 10</td>
<td>590 935</td>
<td>590 935</td>
</tr>
<tr>
<td>Novel Macrolides 11</td>
<td>1 585 074</td>
<td>1 585 074</td>
</tr>
<tr>
<td>Dihydroorotate Reductase (SHTRT) 12</td>
<td>682 958</td>
<td>680 537</td>
</tr>
<tr>
<td>TDN Pharmacospina HDS 13</td>
<td>689 058</td>
<td>680 400</td>
</tr>
<tr>
<td>Pyrimidine Pro-drugs 14</td>
<td>67 504</td>
<td>67 504</td>
</tr>
<tr>
<td>Quinoline Methanols 15</td>
<td>71 048</td>
<td>71 048</td>
</tr>
<tr>
<td>Falciparum Support 16</td>
<td>256 237</td>
<td>256 237</td>
</tr>
<tr>
<td>Immucilacta - HDPRT 17</td>
<td>243 144</td>
<td>233 144</td>
</tr>
<tr>
<td>Queensland Natural Products Medicinal Chemistry 18</td>
<td>518 331</td>
<td>518 331</td>
</tr>
<tr>
<td>Quinoloids and Tetracyclines 19</td>
<td>49 225</td>
<td>49 225</td>
</tr>
<tr>
<td>Niche Biodiversity Antimalarials 20</td>
<td>383 262</td>
<td>183 262</td>
</tr>
<tr>
<td>DODP Pathways Targets 21</td>
<td>16 501</td>
<td>16 501</td>
</tr>
<tr>
<td>Rutgers Natural Product Program 22</td>
<td>49 674</td>
<td>0</td>
</tr>
</tbody>
</table>

#### DISCOVERY MINI-PORTFOLIOS

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>8 969 893</td>
<td>8 821 985</td>
<td>148 028</td>
</tr>
<tr>
<td>GSK (Mini-portfolio T) 23</td>
<td>2 573 508</td>
<td>2 573 508</td>
</tr>
<tr>
<td>Novartis (Mini-portfolio 2) 24</td>
<td>183 620</td>
<td>183 620</td>
</tr>
<tr>
<td>Broad Genzyme (Mini-portfolio 3) 25</td>
<td>1 378 000</td>
<td>3 590 022</td>
</tr>
<tr>
<td>Queensland Screens (Eskitis) 26</td>
<td>757 215</td>
<td>757 215</td>
</tr>
<tr>
<td>Target Screening Program at GNF-NITD (Screening portfolio) 27</td>
<td>1 137 500</td>
<td>1 137 500</td>
</tr>
</tbody>
</table>

#### NEW CONSORTIA SUPPORTING THE ERADICATION AGENDA

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1 137 565</td>
<td>1 137 565</td>
<td>0</td>
</tr>
<tr>
<td>Gametocystic Assay Development and Screen (HTS) 28</td>
<td>317 298</td>
<td>317 298</td>
</tr>
<tr>
<td>Liver Stage Assays (SEB) 29</td>
<td>381 023</td>
<td>381 023</td>
</tr>
<tr>
<td>Artemisinin - Drug Resistance/Surveillance 31</td>
<td>445 244</td>
<td>445 244</td>
</tr>
</tbody>
</table>

#### ENABLING PROJECTS

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>2 672 463</td>
<td>2 561 987</td>
<td>0 076</td>
</tr>
<tr>
<td>Artemisinin Plant Optimisation 32</td>
<td>884 875</td>
<td>798 783</td>
</tr>
<tr>
<td>GSK Support Group 33</td>
<td>785 488</td>
<td>785 488</td>
</tr>
<tr>
<td>Antibacterial Drug Screening at the Swiss Tropical Institute (STI) 34</td>
<td>876 197</td>
<td>873 746</td>
</tr>
<tr>
<td>Construct DHODH Projects 35</td>
<td>74 830</td>
<td>74 830</td>
</tr>
<tr>
<td>Kinase Library Screen 36</td>
<td>36 169</td>
<td>36 169</td>
</tr>
<tr>
<td>Natural Product Technologies 37</td>
<td>15 000</td>
<td>15 000</td>
</tr>
</tbody>
</table>

#### WIND-DOWN COSTS - TERMINATED PROJECTS

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>288 786</td>
<td>263 286</td>
<td>5 500</td>
</tr>
<tr>
<td>RBHIT IBD 38</td>
<td>83 723</td>
<td>83 223</td>
</tr>
<tr>
<td>PSAC 39</td>
<td>203 663</td>
<td>0</td>
</tr>
</tbody>
</table>

**GRAND TOTAL**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>40 285 879</td>
<td>34 238 481</td>
<td>6 047 419</td>
</tr>
</tbody>
</table>

### PROJECT PARTNERS

1. Novartis Pharma AG, Switzerland
2. Prince Léopold Institute of Tropical Medicine, Belgium; EDCTP**, the Netherlands
3. University of Iora, USA; Shion Pharmaceutical Co. Ltd., South Korea
4. Sigma-Tau Industrial Farmaceutica Rovisa S.A., Italy
5. GSK/DMHN (GSK), UK; University of Liverpool, UK; WHO/TDR, Switzerland
6. MMV, Switzerland; University of Tübingen, Germany; EDCTP**, the Netherlands
7. MMV, Switzerland; Hong Kong-University of Science & Technology, Hong Kong
8. GSK, UK
9. GSK, UK; University of Liverpool, UK
10. GSK, UK
11. MMV, Switzerland; University of Nebraska Medical Center, USA; Monash University, Australia; Swiss Tropical Institute (STI), Switzerland
12. MMV, Switzerland; Trogue Limited, UK
13. Walter Reed Army Institute of Research (WRAIR), USA
14. BioCryst Pharmaceuticals, Inc., USA
15. University of Texas Southwestern Medical Center, USA; Monash University, Australia; University of Washington, Seattle, USA
16. GSK, Croatia; GSK, Tres Cantos, Spain
17. University of Nebraska Medical Center, USA; Monash University, Australia; STI, Switzerland
18. NTIDBA (NTIDC), Thailand; London School of Hygiene & Tropical Medicine (LSHTM), UK; Monash University, Australia
19. WHO/TDR, Switzerland
20. University of Washington, USA
21. WRAIR, USA; Monash University, Australia; Dundee University, UK
22. University of California at San Francisco (UCSF), USA
23. Albert Einstein College of Medicine of Yeshiva University, USA; Industrial Research Laboratory, New Zealand
24. Exakis Institute for Cell & Molecular Therapies**; Queensland Institute for Medical Research; Australian Army Malaria Institute; Monash University, Australia
25. University of South Florida (USF), USA
26. USF, USA
27. Texas A&M University, USA
28. Rutgers University, USA; University of Cape Town, South Africa; North Carolina State University, USA
29. GSK, Tres Cantos, Spain
30. Novartis Institute for Tropical Diseases (NITD), Singapore
31. Broad Institute of MIT and Harvard, USA; Genzyme Corporation, USA
32. Exakis Institute for Cell & Molecular Therapies**, Australia
33. NITD, Singapore; Genomics Institute of the Novartis Research Foundation, San Diego, USA
34. Exakis Institute for Cell & Molecular Therapies**, Australia
35. Seattle Biomedical Research Institute (SBIR), USA
36. STI, Switzerland
37. FSC Nova, USA; Bath City, Bions Ltd, Kentech Technologies Ltd, Cranfield Uni., Cord Ltd, Colm Hill Ltd, UK; Mediplant, Switzerland
38. GSK, Tres Cantos, Spain
39. STI, Switzerland
40. University of Texas Southwestern Medical Center, USA
41. University of Dundee, UK
42. University of Mississippi, USA
43. MMV, Switzerland; Ranbaxy Laboratories Ltd, India
44. National Institutes of Health (NIH), USA
45. European and Developing Countries Clinical Trials Partnership; ** Griffith University

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*European and Developing Countries Clinical Trials Partnership; ** Griffith University
7. PROJECT-RELATED VARIABLE EXPENDITURE, CONTINUED

Project-related variable expenditure represents the awards to the projects as specified above, directly managed and supervised by MMV. It also includes all legal advice/services for contract negotiations (IPR), organization and travel for project meetings/reviews, MMV scientific personnel compensation and various scientific project consultancies.

Expenditure for this MMV support totalled USD 5,332,516 and USD 4,282,992 in 2008 and 2007, respectively.

For more details refer to Success Highlights (page 6).

Project balance reimbursements

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

Salaries and related charges are included under Project-related Variable Expenditure, Access-related Variable Expenditure and Staff-related Benefits/Compensation.

There were 33 employees at 31 December 2008 (2007: 23).

During 2007, the Swiss Institute of Certified Accountants reviewed accounting for benefit plans in Switzerland and concluded that generally those plans qualify as defined benefit plans. In this context, MMV has reviewed its pension plan and has determined that it should be accounted for as a defined benefit plan.

As of 1 January 2007, MMV has recorded an adjustment to its opening reserves of USD 566,888 to reflect the net accumulated benefit obligation of its pension plan as of that date.

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.

9. FINANCIAL INCOME (EXPENSE), NET

<table>
<thead>
<tr>
<th>Financial Income (Expense), Net</th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interest income</td>
<td>968,608</td>
<td>1,110,422</td>
</tr>
<tr>
<td>Financial expense</td>
<td>21,038</td>
<td>22,718</td>
</tr>
<tr>
<td>Net exchange gain</td>
<td>247,492</td>
<td>200,333</td>
</tr>
<tr>
<td><strong>NET INCOME</strong></td>
<td><strong>1,195,094</strong></td>
<td><strong>1,288,839</strong></td>
</tr>
</tbody>
</table>

10. LEASES

Non-cancelable operating lease rentals are payable as follows:

<table>
<thead>
<tr>
<th>Lease Term</th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than one year</td>
<td>508,041</td>
<td>386,441</td>
</tr>
<tr>
<td>Between one and five years</td>
<td>1,850,732</td>
<td>732,862</td>
</tr>
<tr>
<td>More than five years</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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 2008, USD 503,605 were recognized as an expense in the statement of income and expenditure in respect of operating leases (2007: USD 401,087). Lease expenses are included under “Office & Occupancy” in the statement of income and expenditure.

11. CONTINGENT ASSETS

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

<table>
<thead>
<tr>
<th>Contingent Asset Type</th>
<th>2008 (USD)</th>
<th>2007 (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than one year</td>
<td>21,500,000</td>
<td>48,800,000</td>
</tr>
<tr>
<td>Between one and five years</td>
<td>20,802,000</td>
<td>38,302,000</td>
</tr>
<tr>
<td>More than five years</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

12. RELATED PARTIES

MMV has a related party relationship with its board members and executive officers. In addition to their salaries, the organization also contributes to a defined benefit pension plan for all staff on a ratio of 7½% employer and 2½% employee.

Total remuneration is included in Project-related Variable Expenditure, Access-related Variable Expenditure and Staff-related Benefits/Compensation in the statement of income and expenditure.

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.

There were no loans to directors or executive officers for the year ended 31 December 2008 and 31 December 2007.

13. FINANCIAL RISK MANAGEMENT

MMV has exposure to the following risks from its use of financial instruments:

- Credit risk
- Liquidity risk
- Market risk

This note presents information about MMV’s exposure to each of the above risks and MMV’s objectives, policies and processes for measuring and managing risks.

Credit risk

Credit risk is the risk of financial loss to MMV if a customer or counterpart to a financial instrument fails to meet its contractual obligations, and arises principally from exposure to MMV donors and investments.

The philosophy underlying MMV financial management is that of prudent, conservative control, including an appropriate return on interim treasury investments. Such investments serve to maintain the value of the funds donated to the foundation until such time as they are used for the aims and objectives as defined in the statutes. MMV limits its exposure to credit risk by only investing in bank time deposits and only with counterparties that have a credit rating of at least A from Standard & Poor’s or Moody’s.

At the balance sheet date there were no significant concentrations of credit risk.

The maximum exposure to credit risk is represented by the carrying amount of each financial asset in the balance sheet, principally accounts receivable, short-term deposits and cash.

As at 31 December 2008, there were no significant capital expenditure commitments. As a condition to MMV’s business credit card relationship with its bank it has signed the bank’s general terms and conditions agree-
ment. This agreement requires that MMV pledge certain of its assets to secure unpaid credit card transactions for a total amount of CHF 200,000 (2007: CHF 100,000)

Liquidity risk
Liquidity risk is the risk that MMV will not be able to meet its financial obligations as they fall due. MMV’s approach to managing liquidity is to ensure, as far as possible, that it will always have sufficient liquidity to meet its liabilities when due, under both normal and stressed conditions, without incurring unacceptable losses or risking damage to MMV’s reputation.

Market risk
Market risk is the risk that changes in market prices, such as foreign exchange rates and interest rates will affect MMV income or the value of its holdings of financial instruments. The objective of market risk management is to manage and control market risk exposures within acceptable parameters.

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

15. 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 financial statements, despite the fact that the outcomes of these uncertainties can not 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.
2009 is a landmark year for MMV

Not only is it the tenth year of our existence, but at the very start of the year we were proud to launch the first-ever MMV-supported product registered by a stringent regulatory authority – a paediatric, cherry-flavoured, sweet, dispersible formulation, Coartem® Dispersible. Press briefings and symposia were held in Basel, Switzerland; Dar es Salaam Tanzania; Maputo, Mozambique; and Dakar, Senegal; and enormous interest was generated worldwide for this new formulation that will save the lives of countless children suffering from malaria.

MMV’s annual Stakeholders’ Meeting will take place in Dakar, Senegal in June. The Stakeholders’ Meeting is attended by representatives of MMV’s donor organizations as well as industrial and academic partners from around the world. Last year, this meeting was held in Accra, Ghana.

This summer, MMV is expecting to submit registration files for Pyramax and Eurartesim to a stringent regulatory authority. Approval will pave the way for the launch of these two new drugs in 2010.

A festive evening to mark MMV’s 10th anniversary will take place in Geneva to convey our heartfelt appreciation to all MMV supporters and partners. The event will celebrate a decade of excitement, achievement and challenges. Ten years of progress, ten years of success, ten years of growth. Without the unwavering belief of our supporters in MMV’s mission and capability we would not have built the largest-ever malaria drug portfolio, nor would we have established ourselves as experts in the field of antimalarial access and delivery. Invitees will include MMV Board members, scientific advisors, industrial and academic partners, and donors.