Developing next-generation medicines

Overcoming resistance

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

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

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

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

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

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

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

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

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

We developed the assay, which we call the ring-stage survival assay, RSA0-3h and were really excited to see that OZ439 is active. Further work has shown just how strongly associated the results are to clinical data. We see a high survival rate of parasites from patients with a slow parasite clearance rate and vice versa. We are now able to characterize and distinguish resistant and sensitive parasites in the lab.

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

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

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

**Q** How was the molecular marker for artemisinin resistance identified?

Colleagues at Institut Pasteur in Paris sequenced a parasite strain that had been cultured under pressure and became resistant to artemisinin. We then compared the genomes of this strain with its parent (non-exposed to artemisinins) and found mutations in eight genes that could be involved in drug resistance. In Cambodia, we then checked to see if these genes were also mutated in isolates from patients. We found that only mutations in one gene (Kelch gene on the chromosome 13 [named K13], which is clearly associated with artemisinin resistance) were expressed in the new in vitro assay (RSA0-3h).

In Pailin, on the Thai-Cambodia border, we have seen an increase in the mutant parasite since 2002, which coincides with the increase in artemisinin resistance. While in provinces without delayed parasite clearance time, we see parasites with no mutation in the K13 gene.

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It was very easy to work with MMV. The people are smart and we share the same goal: to get results. The lab is tough; you can’t just push a button and get results. They understand that. Our job is to characterize drug resistance, raise the issue, and develop tools to detect it. With MMV, we also have the possibility to help develop a solution: next-generation antimalarials that are effective against the resistant parasites.

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

(OZ439) To me it’s a wonderful molecule. It’s very efficient against artemisinin-resistant parasites and works quickly and efficiently.
n 2014, our front-runner compounds with single-exposure potential continued to progress through the pipeline, taking us closer to a next-generation antimalarial treatment.

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

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

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

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

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

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

How will you overcome these challenges?

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

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

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

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

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

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

What’s the effect of malaria on families and communities?

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

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

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

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

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

Trifhonia’s story, Malawi

Trifhonia Idrissah lives near Blantyre, Malawi, with her husband and four children. Her children suffer from malaria up to six times a year. To make a living, Trifhonia sells duvets, shoes and clothes. When one of her children is sick with malaria she can’t work. She spends time and money caring for her sick child and worries about not being able to provide for the others.
KAE609

Patient exploratory (phase II)

Target indication: Part of a combination treatment for acute uncomplicated malaria

Key features:
- Novel acting with potential to treat artemisinin-resistant strains of malaria
- Potential for a single-exposure treatment in combination with a partner drug
- Rapid parasite and fever clearance in uncomplicated malaria patients
- Potential to kill gametocytes and block transmission

Project Leader: Dr Giancarlo Francese, Novartis Pharma AG
MMV Project Director: Dr Isabelle Borghini-Fulter
Development partner: Novartis Pharma AG
Discovery partners: Novartis Institute for Tropical Diseases, Singapore; The Wellcome Trust, UK; Swiss Tropical and Public Health Institute, Switzerland; Biomedical Primate Research Institute, the Netherlands; Genomics Institute of the Novartis Research Foundation, USA

KAF156

Patient exploratory (phase II)

Target indication: Part of a combination treatment for acute uncomplicated malaria

Key features:
- In vitro activity against liver schizonts and potential for chemoprophylaxis
- Potential for a single-exposure cure and therefore improved patient adherence to treatment

Project Leader: Dr Roger Waltzmann, Novartis Pharma AG
MMV Project Director: Dr Jörg Mörhle
Development partner: Novartis Pharma AG
Discovery partners: Genomics Institute of the Novartis Research Foundation, USA; the Wellcome Trust, UK; Swiss Tropical and Public Health Institute, Switzerland; Biomedical Primate Research Institute, the Netherlands

DSM265

Patient exploratory (phase II)

Target indication: Part of a combination treatment for acute uncomplicated malaria

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

Project Leader: Dr Thomas Rueckle, MMV
Partners: University of Texas Southwestern, USA; University of Washington, USA; Monash University, Australia; AbbVie, USA; Takeda Pharmaceutical Company Ltd, Japan

MMV048

Human volunteers (phase I)

Target indication: Part of a combination treatment for acute uncomplicated malaria

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

Project Leader: Dr Cristina Donini, MMV
Partners: University of Cape Town, South Africa; Technology Innovation Agency (TIA), South Africa

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DSM265 is a triazolopyrimidine-based highly selective inhibitor of P. falciparum’s dihydroorotate dehydrogenase (DHODH), a key enzyme for the parasite’s survival. In January 2015, the compound entered a phase IIa clinical trial in Iquitos, Peru. Here, its activity in both P. falciparum and P. vivax malaria patients is being put to the test. Preliminary results from the trial are very encouraging.

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

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

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

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

It has a big impact, as morbidity is very high. Patients are not able to work or perform their regular activities when they are suffering. They lose many days of work and many of them suffer repeatedly.

People usually have infection several times per year; in many cases five times a year or even as much as 10 or 20 times.

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

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

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

Q: What would be the ideal antimalarial medicine for Peru?

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

Q: What is unique about DSM265?

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

Q: What is special about this study?

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

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5. With support from the German Center for Infection Research (DZIF).
6. With support from the United States Department of Defense.
7. With support from the Global Health Innovation Technology (GHIF) Fund.
Dr Phumla Sinxadi 
Clinical Pharmacologist at UCT and Lead Investigator for the MMV048 study, explains the goal of phase I studies and how MMV048 is progressing.

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

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

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

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

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

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

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

**Tafenoquine**

Patient confirmatory (phase III)

Target indication: prevent relapse of *P. vivax*

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

Project Leader: Dr JP Klein, GSK, UK

MMV Project Director: Dr Wiweka Kaszubska

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**ISSUE**

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

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**ACTION BY MMV AND PARTNERS**

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

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Tafenoquine is currently in phase III development with GSK. The aim is to investigate its potential as a single-exposure medicine to prevent the relapse of *P. vivax* malaria, with the current intention of submitting a new drug application to the US FDA\(^2\) in 2017. If successful, it would be the first new medicine for relapsing malaria to progress to regulatory approval in over 60 years.

Tafenoquine would be used alongside a blood-stage medicine, which together would cure the current malaria infection and prevent a future relapse.

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

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

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

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

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

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

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

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

Rithsankan’s story, Cambodia

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

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

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

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

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

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

Q How is the team working to overcome these challenges?

By working in partnership. We are collaborating with MMV, PATH and the Gates Foundation to co-create a patient access plan. This includes thinking through how tafenoquine and a G6PD-deficiency test could be introduced in close consultation with malaria-control programme managers, experts and WHO.

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

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

Once tafenoquine and a point-of-care test have been approved for use, we will continue to work in partnership and solicit greater involvement from the malaria community. GSK and MMV are developing this medicine to meet the needs of populations afflicted by P. vivax malaria. Our objective is to have tafenoquine widely available and affordable in malaria-endemic countries. That’s what is driving us. GSK intends to provide the medicine at an affordable price to enable wide patient access in these countries.

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

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

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