### Developing new medicines for case management and vulnerable populations

**Addressing the dual challenges of resistance and compliance**

#### ISSUES

Artemisinin-based combination therapy (ACT) is the WHO-recommended first-line treatment for malaria. However, malaria parasites have emerged that are resistant to both artemisinin and partner drugs, and these have the potential to spread. Without effective new medicines, the malaria burden and mortality may rise.

ACTs must be taken once or twice daily over a period of 3 days but poor treatment compliance leads to incomplete cure, which contributes to the emergence of drug-resistant malaria parasites. 

#### ACTION

MMV and partners are identifying and developing novel compounds active against all known resistant parasite strains that could potentially be administered as a Single Encounter Radical Cure (SERC) – a single-dose treatment. A SERC could increase patient compliance, combat the threat of future drug resistance and, with added chemoprotective activity, could ultimately support mass drug administration campaigns for elimination.

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**Table 1: A Multi-Encounter Radical Cure and Prophylaxis (MERCaP)**

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**Malaria parasites that are resistant to artemisinin and its partner drugs, mefloquine and piperaquine, have emerged in the Greater Mekong Subregion (GMS), resulting in high levels of treatment failure.**

Signs of potential reduced sensitivity and/or treatment failure with ACTs have also been reported in several patients who contracted malaria in Africa. These preliminary signs indicate that the global community must remain vigilant to the possible emergence of artemisinin resistance outside the GMS. In a worst-case scenario, malaria could become untreatable without new and effective therapies at hand.

MMV and partners have prioritized the development of new treatments (see Table 1) to address the dual challenges of drug resistance and treatment compliance, by identifying molecules with novel mechanisms of action and activity against all known resistant parasite strains that could potentially be given as a SERC. The new molecules either kill the parasite quickly; stay in the body long enough to ensure complete parasite clearance; and/or can protect against subsequent reinfection.

The longer-term aim is to develop a Single Encounter Radical Cure and Prophylaxis (SERCaP; page 8) that would also provide chemoprotection and be suitable for use in mass drug administration programmes. A Multiple Encounter Radical Cure (MERCo) Multiple Encounter Radical Cure and Prophylaxis (MERCaP) that demonstrates efficacy against key resistant strains would also have utility.

In the interviews that follow, MMV’s scientists and partners report on recent progress to develop these next-generation medicines.
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**Table 1: Activity of MMV-supported molecules in development, 2016**

GNF: Genomics Institute of the Novartis Research Foundation; SERC: Single Encounter Radical Cure; Swiss TPH: Swiss Tropical and Public Health Institute.
A single-dose cure could make a big difference both to the individual patient and to the population as a whole.
Artefenomel (OZ439) plus ferroquine

Artefenomel, a novel trioxolane, is a front-runner candidate for inclusion in a new antimalarial combination with ferroquine. The combination is being specifically formulated for children and to allow for once-daily dosing. However, achieving an equivalent efficacy and safety profile in fewer doses than current 3-day ACT regimens is a major challenge. In partnership with Sanofi, MMV is aiming to overcome that challenge. The combination is currently in a phase IIb trial, which is expected to be completed in the fourth quarter of 2018.

Dr Laurent Fraisse talks about the added value of the combination as well as the advantage of working with MMV.

What could artefenomel plus ferroquine offer to the current antimalarial arsenal?

"First, it would be a new-generation antimalarial combination, potentially the first not directly based on artemisinin derivatives. Given what we currently know about each compound, we are optimistic the combination will be effective against current resistant strains of malaria, although we don’t yet have clinical data to confirm this. It could therefore provide an alternative to current treatments and stop the progression of malaria to severe disease.

Second, the phase IIb trial is being conducted entirely with the combination as a single dose. Based on the blinded interim results generated so far, we are very optimistic. I believe a single-dose cure could make a big difference both to the individual patient and to the population as a whole. For patients, we know they will receive a complete cure. For the population, a complete cure decreases the chance of drug resistance emerging. Without a doubt, this is an important project in Sanofi’s portfolio."

What are the next steps?

"The next step will be an interim analysis of the phase IIb trial data expected in mid-2018. This will help us determine the best dose ratio between artefenomel and ferroquine. So far, we have assessed several doses of ferroquine in combination with one dose of artefenomel in adults. For the moment, it looks like all the doses are effective, but of course it’s all very preliminary data so we have to wait and see. The trial has been designed to enable us to test the drug combination in the younger population once the safety is established in the older age groups."

What is the added value of working with MMV on this project?

"Working with MMV makes this possible as we share both risk and cost, and leverage the strengths and expertise of each organization to its full potential. MMV and its scientific committee are respected experts in the field of malaria research. Internally at Sanofi, we have other strengths but less malaria expertise, so to receive feedback from the senior scientists on MMV’s scientific committee is really important and vital to the success of the project. It’s also good to partner with a smaller organization like MMV that has the ability to be nimble in addressing issues and challenges that arise. At times, there can be differences of opinion that require adaptability on both sides, but ultimately the project benefits from the diverse expertise and culture the two organizations bring. As a result, we probably progress faster and the likelihood of success is much greater.

Finally, as MMV has a global view of malaria drug development, working in partnership guarantees that what we develop together will have enormous value for the patient."

What is the biggest challenge in the development of the combination?

"The main challenge is the formulation. How can we provide a sufficient quantity of drug for a complete cure in one single dose in children and adults? How do we combine the two drugs and ensure optimal absorption? These are some of the questions we are working to resolve to ensure continued development of this exciting combination."

Dr Laurent Fraisse
Vice President
Infectious Diseases R&D,
Sanofi
KAF156 belongs to a novel class of antimalarial molecules, the imidazolopiperazines, and in phase IIa trials was able to rapidly clear both *P. falciparum* and *P. vivax* parasites. On this basis, in 2017, KAF156 will enter phase IIb combination studies with the antimalarial lumefantrine.

MMV and Novartis are working together to develop the combination. The partnership builds on an already solid and successful history of collaboration in antimalarial drug development, which in 2009 led to the launch of the first high-quality artemisinin combination therapy for children.

David Hughes talks of the promise that KAF156 holds as a future antimalarial, as well as the path ahead to help realize that promise.

**What is exciting about KAF156 as a potential antimalarial?**

KAF156 is potent across multiple stages of the parasite lifecycle, which means it has the potential not only to cure the clinical symptoms of malaria in a single dose but also to block its transmission, thus protecting people from actually contracting the disease in the first place.

It also appears to be active against current resistant strains of the parasite. There are real concerns around the emergence of resistance in the field to both artemisinin and its partner drugs, which have been reported in Asia. Recently, we have begun to see the first potential signs of reduced sensitivity to artemisinin in Africa. The sooner we can have compounds that are effective against resistant parasites the better.

**What are the plans for the phase IIb study?**

The phase IIb study is due to start in July 2017. We will be testing KAF156 as a once-daily administration for 1, 2 and 3 days. In many respects, it’s set to be a ground-breaking trial, employing a number of adaptive trial design features. The study will characterize different combinations of KAF156 and lumefantrine, for different durations, in different patient groups (adults, adolescents and children).

As the treatment of children represents the biggest unmet need, the goal is to begin including them in the clinical trial as quickly as possible. We’ve really tried to think through scenarios to accelerate the drug’s development while ensuring patient safety and we’re confident the design chosen will achieve this.

**Why was lumefantrine chosen as the partner drug for the phase IIb study?**

Lumefantrine is a tried and tested antimalarial. It has been used in combination with artemisinin in Coartem® for a number of years as a very effective standard-of-care, particularly in sub-Saharan Africa. In addition, we have been able to reformulate it to allow once-a-day dosing for multiple days.

**For a large pharmaceutical company like Novartis, what is the advantage of working with MMV?**

Novartis and MMV not only have a long-standing history of successful collaboration in malaria research, but we also have some very complementary skills and experiences. MMV’s international network of partners provides an efficient way for us to quickly access clinical experts, both from academia and MMV’s own staff, and we benefit from MMV’s advice to complement our own experience on operational aspects of how and where to conduct clinical trials. In addition, MMV provides effective access to other third-party funders who want to contribute to the global fight against malaria.

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1. KAF156 is the result of a Wellcome Trust, MMV and Singapore Economic Development Board-supported joint research programme with the Genomics Institute of the Novartis Research Foundation, the Novartis Institute for Tropical Diseases, the Netherlands Primate Research Centre and the Swiss Tropical and Public Health Institute.
DSM265

DSM265 has the potential to both treat and protect against malaria in a single dose. The compound selectively inhibits a vital enzyme (dihydro-orotate dehydrogenase; DHODH) in the malaria parasite essential for its survival, while the human enzyme remains unaffected at and beyond therapeutic concentrations.

The compound successfully demonstrated safety and efficacy against *Plasmodium falciparum* in a phase IIa trial in malaria patients in Peru, and the data is expected to be published in 2017. Phase III trials in combination with a partner drug/drugs are planned to further confirm this activity.

DSM265 is being developed with Takeda Pharmaceutical Company Limited, headquartered in Japan, with funding from the Global Health Innovative Technology Fund (GHIT) and *pro bono* support from AbbVie.

Prof. Alejandro Llanos-Cuentas, Principal Investigator for the phase IIa study in Peru talks about the trial, the challenges of managing malaria in Peru and how DSM265 could help address them.

What was the biggest challenge you faced during the study and how did you overcome it?

“For the people of the Amazon, malaria is not a disease considered to require hospitalization, especially as their livelihood and ability to provide for their families depends heavily on their ability to work. Originally the protocol planned for 3 days of observation of patients in the clinic following treatment, but in practice at times we needed to keep them in for longer. In these cases, it was challenging to convince them stay. To overcome this, we spent additional time explaining the situation and the importance of the study to patients and their families and where necessary provided them with housing and food.”

What are the main challenges in managing malaria in Peru?

“Recently, there has been a resurgence of both *Plasmodium vivax* and *P. falciparum* malaria in Peru. Between 2005 and 2011, a malaria control programme was implemented with economic support from the Global Fund, which led to an 80% decrease in cases (11,000 cases were reported in 2011). However, 2 years later in 2013, the number increased to around 40,000 and then to 60,000 in 2014. Unfortunately, these increases are no longer the exception but the rule.

The causes range from lack of adequate antimalarial medicines and a lack of knowledge, as well as competing government priorities leading to inaction. Through studies conducted by our group in recent years in the Peruvian Amazon, we find we have a large number of people with asymptomatic or subpatent malaria, who carry the disease but are themselves not sick and so don’t seek treatment. This mass of people act as a reservoir for the transmission of infection and are a serious challenge to malaria elimination since they are difficult to identify, diagnose and treat.”

What is exciting about DSM265 as a future antimalarial, particularly in the Peruvian context?

“In combination with another medicine, DSM265 could be an excellent prospect for both asymptomatic and subpatent *P. falciparum* malaria because it could potentially be used as a single dose. This would be a key tool to eliminate malaria in endemic regions like the Amazon.”

What was it like working with MMV on this study?

“The experience was very good. MMV and its people have a genuine concern to find new therapeutic solutions for malaria.”

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1 People with asymptomatic malaria carry a low level of malaria parasites, as confirmed by thick blood smear test using optical microscopy, but don’t have any symptoms.
2 People with subpatent malaria infections carry an even lower level of malaria parasites, they test negative for malaria via a rapid diagnostic test and thick blood smear but positive by polymerase chain reaction.
MMV048 is a novel antimalarial compound from the aminopyridine class, with important activity across the entire parasite lifecycle. The compound was researched by an international team led by Prof. Kelly Chibale from the University of Cape Town, South Africa and was the first new antimalarial medicine to enter phase I studies in Africa.

Dr Cristina Donini explains her vision for MMV048, as well as the importance of getting the formulation right and building clinical trial capacity in Ethiopia.

**What is your vision for MMV048?**

“MMV048 has the potential to become part of a single-dose cure for uncomplicated malaria. One single dose would simplify malaria treatment and therefore increase compliance. The compound also has a novel mechanism of action that could help fight emerging drug resistance. If all this potential is confirmed, MMV048 could become part of a major tool for malaria elimination and eradication efforts.”

**What are the next steps?**

“The next step is the phase IIa clinical trial in patients as a single dose. The trial will begin in July 2017 in Ethiopia in adults with mono-infection of either *P. falciparum* or *P. vivax* malaria. To conduct this trial, we are working with Prof. Harald Noedl, of the University of Vienna, to strengthen the research capacity at two health facilities on the outskirts of Gondar and Jimma in Ethiopia. We are in the midst of building two dedicated patient wards and purchasing new equipment and lab supplies as well as training local staff in good clinical practice.

In parallel, we are looking at MMV048’s potential ability to protect against malaria infection. This will be tested in the Controlled Human Malaria Infection (CHMI) model (pages 24–25), which is similar to the models that are used to test vaccines.”

**Why was the formulation development so critical to the project?**

“The previous formulation provided too much variability in exposure, which would lead to inconsistent dosing in patients and therefore not be consistently effective; this could pose a safety issue. It was critical to find a new formulation with less variability to be able to pursue the project.”

**What’s exciting about this project for you?**

“This is a multifaceted project. We are not only developing a new medicine for malaria but also strengthening local research capacity and fostering lasting collaborations between European and African institutions. In the future, this capacity could be used for clinical trials for malaria as well as other diseases of poverty.”
Prioritizing molecules suitable for pregnant women

Malaria is more common and severe in pregnant women than in non-pregnant women, increasing their risk of miscarriage and other adverse outcomes. Every year, up to 125 million pregnancies around the world are at risk from malaria, while 10,000 pregnant women and 200,000 new-borns die as a consequence of the disease.¹

The adverse consequences of malaria in pregnancy demand prompt, well-tolerated and effective treatment. Current WHO guidelines allow the use of artemisinin-based combination therapies (ACTs) for women with malaria in the second- and third-trimester of pregnancy. To date, there are no treatment recommendations for the first trimester, when the fetus is most vulnerable, owing to a historical absence of key safety data. This may be set to change. A recent meta-analysis of all observational studies to date has demonstrated that the risk of miscarriage, stillbirth or major birth defects associated with ACTs during the first trimester, was the same as for quinine.²

With both the mother and baby’s lives at risk, WHO recommends that pregnant women living in areas of moderate-to-high malaria transmission should receive the drug sulfadoxine-pyrimethamine (SP) as Intermittent Preventive Treatment in Pregnancy (IPTp).³,⁴ However, drug resistance to SP and signs of its declining efficacy are causing concern. With no suitable alternatives available, some experts have suggested ACTs could also be used as chemoprevention in pregnancy. Yet, this would lead to the dilemma of the same medicines being used for both chemoprevention and treatment – a situation not typically recommended by WHO because of concerns such as drug resistance, which may more likely ensue owing to the additional drug pressure.

New and distinct antimalarial medicines that are suitable for pregnant women are urgently needed for both treatment and protection, but their development is extremely challenging.

Generally, pregnant women are excluded from clinical trials of new drugs until the risks and benefits are well understood first among non-pregnant adults; however, drug dosing can differ between these groups.

While we cannot definitively predict which medicines will be suitable during pregnancy, we can identify those which would not. Traditionally, preclinical studies to determine if a molecule would have an adverse effect in pregnancy/on the fetus are conducted in parallel with phase II studies. MMV has developed a strategy to move this testing forward so it is run in parallel with phase I. This strategy has been implemented for the last three development candidates (MMV048, DSM265 and P218).

We now propose to carry out these tests routinely before clinical development, to identify unsuitable medicines as early as possible. This will allow resources to be focused on molecules that are more likely to be safe in later development and to have eventual routine clinical use in pregnant women.

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⁴ IPTp is the administration of a full course of an effective antimalarial treatment. It should only be administered to pregnant women living at risk of malaria after their first trimester and at a minimum of 1-month intervals.
Aiming to stop relapsing malaria with a single-dose treatment

**ISSUE**

The *Plasmodium vivax* malaria parasite is estimated to cause around 8.5 million clinical infections every year.\(^1\) It has the ability to lie dormant in the liver as hypnozoites, which periodically reactivate, leading to a relapse of malaria in the absence of a new infective mosquito bite. Each of the multiple episodes of relapsing malaria keeps a child or adult from school or work for at least 3 days.\(^2\) Studies have shown that beyond lost time, malaria can also have adverse effects on cognitive ability.\(^3,4\) Primaquine is currently the only treatment available to kill the dormant parasites and stop the relapses. WHO recommends its administration once daily for up to 14 days – a regimen that is typically associated with poor compliance.\(^5\)

**ACTION**

MMV and GlaxoSmithKline (GSK) are developing tafenoquine as a potential medicine to prevent *P. vivax* relapse by eliminating hypnozoites from the livers of infected patients with a single dose.

Tafenoquine is an investigational medicine that has completed phase III studies. If approved, it would be the first new medicine for relapsing malaria in over 60 years. Tafenoquine will potentially offer a single-dose cure for the liver-stage of *P. vivax* infections and will be administered alongside a standard 3-day chloroquine or potentially an ACT treatment regimen.

Tafenoquine is a member of the same chemical family as primaquine; both are associated with a risk of haemolytic side-effects in a subset of patients lacking adequate levels of the enzyme glucose-6-phosphate dehydrogenase (G6PD) (on average 8% of people in malaria-endemic countries).\(^6\) To reduce the risk of haemolysis, GSK is working with PATH on the development of a quantitative G6PD point-of-care diagnostic test so that patients’ G6PD status can be tested to determine if tafenoquine or primaquine can be safely administered. The goal is for this field-ready diagnostic test to be available at the same time as the potential launch of tafenoquine in malaria-endemic countries.

Dr Marcus Lacerda has been treating malaria patients in the Amazon since 2000 and was a Principal Investigator for the phase III efficacy trial of tafenoquine in Manaus. He talks about managing malaria in the Amazon and how tafenoquine, if approved, could help.

**What are the biggest challenges in the management and treatment of malaria in the Amazon today?**

*P. vivax* is the big challenge. In Brazil, over the last 20 years the burden of reported malaria cases caused by *Plasmodium falciparum* has come down from 50% to 10−15%.\(^7\) The story is very similar across Latin America. As *P. vivax* doesn’t kill as many people as *P. falciparum*, policy-makers are shifting their attention to other diseases such as Zika and becoming less concerned about malaria. This is a problem because *P. vivax*, which now causes 80–85% of cases, can also be lethal. It also contributes significantly to morbidity and has a substantial economic impact.

In addition we have only one treatment to prevent relapses – primaquine – which in Brazil is administered twice daily for at least 7 days. For various reasons, including poor compliance to treatment, primaquine only works for three out of four people (determined at 6 months’ follow-up). It’s very tough to explain to patients why they should take 7 days of pills to treat something that appears to have resolved after the third day.”

**What role could a new medicine like tafenoquine play in this context?**

Three years ago a plan to eliminate *P. falciparum* malaria in Brazil was released. This was triggered by emerging drug resistance in south-east Asia. But no one has ever considered a *P. vivax* malaria elimination plan because we simply don’t have the tools to address it at the moment. If approved, tafenoquine could potentially change that.”

**What proportion of people in Brazil have G6PD deficiency?**

It depends on the immigration profile. Most published papers on the subject say the average prevalence among men in Brazil is around 5%. In areas where you have more people of African descent, however, the frequency can reach 20–25%.

The Ministry of Health is currently supporting a large survey of the prevalence of G6PD deficiency in the whole population of the Brazilian Amazon and so far, preliminary results confirm it’s around 5%.”
What is the status of G6PD testing in Brazil today?

At the moment patients are not routinely screened for their G6PD deficiency status before they receive primaquine, in fact, nowhere in Latin America does this routinely happen. In some reference centres in Brazil, we have tests which are performed to diagnose deficiency among those who have already haemolysed to help understand why. I would, however, like to see this change and for G6PD testing to become routine.

Dr Justin Green leads the clinical and paediatric teams responsible for the development of tafenoquine. He explains how the work is gathering pace.

How is the phase III programme progressing?

“We have just completed the two studies, DETECTIVE and GATHER, which respectively looked at efficacy and safety. We plan to present the headline results in June 2017 at the 6th International Conference on Plasmodium vivax Research in Manaus, Brazil.”

Why is a paediatric formulation of tafenoquine so important?

“From our perspective, an adult indication is only part of the package. Without a paediatric formulation, I think it’s going to be incredibly challenging for malaria control programmes to have a real impact, particularly in areas of Peru and Brazil, where a lot of children are suffering from relapsing malaria. Thankfully, there is less mortality from P. vivax in children, but morbidity can be high. Persistent infections combined with a poor diet and anaemia lead to children regularly missing school, which in turn results in diminished educational attainment and an additional burden of care on families.”

As a pharmaceutical company, how does GSK benefit from collaborating with MMV?

“Collaboration is key in our efforts to tackle malaria, with each organization bringing different expertise and perspectives. The support and advice we receive from the MMV team and ESAC, as well as access to MMV’s network, is key to the success of the tafenoquine project, particularly given the global nature of the challenge of P. vivax malaria. The expertise that MMV has provided, including the routine checkpoints from ESAC and through the integration of MMV staff into GSK’s core teams, has helped guide the study design and interpretation of data. Such collaborations help advance our research and increase our understanding of new areas of science, while sharing the risks of development.”

Do you foresee any challenges to the combined implementation of tafenoquine and a G6PD test?

“While the situation today is still hypothetical, what we do know is that testing is clearly more cost-effective when compared with hospitalizing people with severe haemolysis.

If tafenoquine becomes available it could potentially improve case management of P. vivax patients and push G6PD testing forward. There will of course be challenges, for example, as the degree of G6PD deficiency varies among patients, we will need to determine the cut-off for when people will be able to receive tafenoquine and when they won’t. Through addressing these challenges we will learn a lot, ultimately, for the benefit of patients.”

6 ESAC: MMV’s independent Expert Scientific Advisory Committee.