

## **Novartis scientists target resistance threat in malaria** <sup>[1]</sup>

### Discovery <sup>[2]</sup>

In a medical treatment facility on the Thai-Burmese border, 21 patients infected with malaria recently participated in a clinical trial. All 21 patients left the facility with no trace of the disease, a finding reported in the July 31 issue of the *New England Journal of Medicine*. That might not sound unusual — several malaria treatments are available — but as the first signs of drug resistance are being seen in Southeast Asia, this trial—while preliminary—showed real promise for novel treatments.

The drug candidate tested during this trial, KAE609, might become one of the first novel treatments to be introduced in decades. It not only showed effectiveness against the two primary malaria causing parasite types, it could be capable of beating drug-resistant malaria as well.

That's welcome news in the fight against this deadly disease that kills more than 600,000 people worldwide each year <sup>[3]</sup>. The problem could get far worse now that the mosquito-borne parasites that carry malaria are showing early signs of resistance to existing antimalarial drugs. The public health consequences could be dire, the World Health Organization (WHO) warns.

## **New antimalarial drugs needed**

This trend is nothing new, however. Malaria parasites have a track record of eventually defeating the drugs that attack them. Chloroquine, which replaced the original treatment, quinine, in the 1940s, lost much of its effectiveness <sup>[4]</sup> after about 40 years. According to the WHO, resistance to artemisinin, the key compound in current standard treatment, has now been detected in Thailand, Myanmar, Cambodia and Vietnam.

“Resistance (to existing drugs) is a given,” says Bryan Yeung, associate director of the malaria program at the Novartis Institute for Tropical Diseases (NITD) <sup>[5]</sup> in Singapore. “It's not a matter of if. It's just when the parasite will become resistant.”

Artemisinin-based combination therapies could become much less effective within the next 10 to 20 years, says Christophe Bodenreider, a key investigator on Yeung's Singapore team.

Novartis, whose researchers developed the new drug candidate given to 21 patients in Mae Sot, Thailand, is fully committed to ensuring a new malaria treatment will be available after regulatory approval.

The company has two drug candidates in clinical development — KAE609 and KAF156 — both of which attack the two parasites responsible for the vast majority of malaria deaths: *Plasmodium vivax*, common in Asia and South America; and the more virulent *Plasmodium falciparum*, most common in Africa. KAE609 is a synthetic “spiroindolone,” which first was identified in Novartis screenings in 2007. KAF156 is an “imidazole piperazine” that the company discovered in 2008.

## Promise seen as new malaria therapy standard

KAE609 is off to an impressive start in clinical trials, and Novartis is studying the feasibility of administering it as a single-dose combination therapy.

“In the clinical trial in Mae Sot, KAE609 was able to clear the blood stages of malaria for all 21 patients, including in those patients with resistant infections,” says Yeung, based on the data.

Now, it's on to the next stage of Phase 2 development, which will include larger-scale human studies, including in Africa.

“Basically we are looking for the magic bullet now, which will be a single dose therapy,” notes Bodenreider in Singapore.

A single dose would help in overcoming challenges associated with multi-dose therapies that threaten the efficacy of today's treatments. For example, some patients who have symptoms decide to hold onto what they see as “extra” pills for the future; others share their medication with family members.

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**Hans Rietveld**, Director, Market Access and Capacity Building, Novartis Malaria Initiative

“When they start to feel better, there's a very strong possibility the patient will stop taking the drug,” notes Kelli Kuhen, a senior research investigator in the United States at the Genomics Institute of the Novartis Research Foundation [6] in San Diego, Calif., which screened the compounds that became the new drug candidates.

Failure to complete the treatment bears two major risks. It may not only cause safety issues for the patient, but can also help targeted malaria parasites develop resistance to the drug.

KAF156, the other drug candidate Novartis has in clinical development, also has a unique potential: Unlike existing malaria drugs — and unlike KAE609 — KAF156 is on track to kill the malaria parasite at its early, asymptomatic liver stage for *P. vivax*. If a drug could wipe out the parasite at that point, the disease would never spread into the blood stream, where it does its worst damage. Thus, KAF156 has a potential to serve as a prophylactic treatment.

“That's the key additional activity for KAF156 that doesn't exist in the current artemisinin based combination therapies,” notes research investigator Case McNamara of GNF. He adds that both drug candidates would have the potential to prevent humans from passing the

parasite to a mosquito which could then infect another human, providing the benefit of reducing the spread of malaria at its source.

Both GNF and NITD are part of the research arm of Novartis called the Novartis Institutes for BioMedical Research, one of whose aims is the discovery and development of affordable drugs and vaccines against neglected infectious diseases, affecting people in the developing world. The work of both Institutes in malaria supports the broader work of the [Novartis Malaria Initiative](#) [7], one of the healthcare industry's largest access-to-medicine programs committed to working toward malaria elimination.

“A decade ago, Novartis set the current gold standard for treatment by launching the first fixed-dose artemisinin-based combination therapy. Today, we have delivered more than 600 million doses without profit to patients in Africa,” says Hans Rietveld, Director, Market Access & Capacity Building, Novartis Malaria Initiative. “But, we need to stay one step ahead of the parasite and drive the development of new antimalarials. It’s rewarding to see that our scientists have built one of the strongest malaria pipelines in the industry and are working so hard to discover next-generation therapies for patients.”

## The quickening pace of drug development

Neither drug candidate might have advanced to its current stage had it not been for the high-tech robots at the Genomics Institute of the Novartis Research Foundation facilities in San Diego that allowed researchers to screen 1.7 million compounds from its library starting in 2006.

Another factor has helped pick up the pace of new antimalarial drug development: an infusion of research funding from organizations such as the [Wellcome Trust](#) [8], the Geneva-based [Medicines for Malaria Venture](#) [9], as well as the partnership of the Basel, Switzerland-based Swiss Tropical and Public Health Institute and the Biomedical Primate Research Centre in The Netherlands. Pending further trials, development and regulatory approval, Novartis could bring both drug candidates to market within the next six years. Meanwhile, a third malaria drug target has recently been identified.

[Read a paper about this research in the New England Journal of Medicine](#) [10]

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