

Experimental treatment clears malaria infections in small clinical study

Compound offers a potential tool for fighting drug-resistant malaria parasites.

By [Elizabeth Dougherty](#) | Oct 31, 2016

In a remote village in Thailand, on the border of Myanmar (formerly Burma), Novartis researchers completed an early-phase clinical trial of an experimental treatment for malaria. The team overcame floods that swamped the facility — an open-air structure with wooden beds and a folding table for a pharmacy — to test a compound called KAF156 in adults with the disease.

In the study, the malaria parasites seemed to quickly disappear from patients who received multiple doses of the compound. The parasites also seemed to disappear from patients who received just a single dose of KAF156, although they later reappeared in some of these patients. The results of the Phase II trial were published [online](#) in The New England Journal of Medicine on September 22, 2016.

The news is welcome because in Southeast Asia there are signs of malaria infections that do not respond well to standard treatments, which often include using a compound called artemisinin in combination with other agents.¹

“Artemisinin resistance was predicted a decade ago, but now we have solid evidence,” says Joel Leong, a translational medicine expert at the Novartis Institute for Tropical Diseases. “It has happened.”

So far, resistance has only emerged in Southeast Asia, but it has been detected in samples 25 kilometers (15 miles) from the border of India in Myanmar and could spread farther. Malaria kills approximately half a million people each year,² most of them children. Without new drugs to treat the disease, this number could begin to rise.

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Nick White, professor at the Mahidol-Oxford Tropical Medicine Research Unit in Bangkok

“In the past, resistance to antimalarial drugs has spread from the Greater Mekong Sub-region and caused millions of deaths in Africa and India,” says Nick White, a professor at the Mahidol-Oxford Tropical Medicine Research Unit in Bangkok and the lead clinical investigator on the KAF156 trial. “The discovery and development of new antimalarial drugs is essential if we are to control and ultimately eliminate malaria. The new drugs must be as safe and effective as those we currently use, and they must not share their resistance mechanisms.”

Testing potential treatments

KAF156 was discovered at the Genomics Institute of the Novartis Research Foundation (GNF) in San Diego, California using robotically assisted high-throughput screening. The GNF team initially tested more than 2 million compounds for antimalarial activity, searching for molecules that could potentially clear both blood and

liver infections, attacking the parasite at both stages of its reproductive life cycle. One of the molecules that stood out looked very different structurally from all known antimalarial drugs. Scientists worked to chemically optimize this molecule, eventually generating the experimental treatment KAF156. It's now being developed as part of the [Novartis Malaria Initiative](#), which is dedicated to providing patients with access to effective treatments.

Leong and colleagues tested KAF156 in 43 patients in five clinics — including the one that flooded — in Thailand and Vietnam. The patients were divided into two groups, allowing the team to explore different dosing regimens.

Outside of carefully controlled clinical settings, malaria patients often fail to complete their full course of treatment. For some treatments, they're instructed to take a pill twice a day for several days. But they often skip pills or stop taking them. And incomplete dosing creates a breeding ground for drug-resistant malaria.

"The ideal would be a drug that is taken once, but anything we can do to make it easier for people to complete treatment is a plus," says Peter Pertel, Global Translational Medicine Head for Infectious Diseases at the Novartis Institutes for BioMedical Research.

In the KAF156 study, the first group of patients received 400 mg of KAF156 once daily for three days. The second group received a single 800 mg dose of the compound.

Promising results

In patients who received three 400 mg doses of KAF156, malaria parasites were eliminated from the blood stream rapidly, within 45 hours for *P. falciparum* malaria, the most deadly form of the disease, and within 24 hours for *P. vivax*, another common strain. As the parasites cleared, patients felt better and their fevers vanished. The experimental treatment even cleared the infection in patients who had tested positive for artemisinin-resistant malaria.

Parasites also disappeared rapidly in patients with *P. falciparum* malaria who received just one dose of KAF156. Although the infection returned in some of these patients, 67% of them remained parasite-free after 28 days.

None of the study participants experienced severe adverse events, but there were side effects reported in most patients, including asymptomatic slow heart rates, nausea, vomiting, and increases in liver enzymes.

The results of this small trial are promising, and Novartis researchers now plan to test KAF156 in combination with another agent among a broader group of patients. They are still working to determine the best possible dosing regimen for the compound. Novartis will lead the next phases of development with scientific and financial [support](#) from the Medicines for Malaria Venture (in collaboration with the Bill & Melinda Gates Foundation).

Remote reinforcements

The connections that the team made during this study, which took place in 2013, will serve researchers and patients well in the future. Since malaria is widespread in rural, tropical areas where the mosquitos that transmit the disease are abundant, that is where trials must be held.

"We have to go where the patients are," says Pertel.

Carrying out a clinical trial in a remote setting requires a significant amount of advance work. For instance,

some of the clinics needed new equipment, such as generators and blood analyzers, to ensure they could produce quality data. The staff also needed training to ensure that procedures for assessing the presence of malaria in the blood would be consistent.

“Several of the sites we’ve worked with have such expanded capabilities now that they’ve gone on to do clinical studies for other companies,” says Leong. “Everyone benefits as a result.” This kind of intervention and partnership would not have been possible without the longstanding success and reputation of the Novartis Malaria Initiative. “Our team and everyone at the Novartis Institute for Tropical Diseases has been working on this for a long time and has built a lot of relationships,” says Pertel. “All that makes these studies easier.”

KAF156 compound offers a potential tool in the fight against drug-resistant malaria parasites #endmalaria

Joining forces to advance public health

Collaborations with people on the ground, like Agnes Akoth, as well as with organizations in the public sector, have been at the core of the Novartis Malaria Initiative from the outset. Today, we are engaged in more than 20 alliances and collaborations that range from research and development, sourcing, production and access, through to distribution and impact assessment.

Learn More

1. http://www.who.int/malaria/media/artemisinin_resistance_qa/en/
2. World Malaria Report 2015

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