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Tackling The Challenge Of Malaria Clinical Trials In Africa

by Kevin Grogan

Novartis leads the fight against malaria, pioneering innovative studies in sub-Saharan Africa to combat parasite resistance to current antimalarials.

Malaria is in the headlines again with Côte d'Ivoire becoming the first country to roll out the new R21 vaccine, co-developed by the University of Oxford and Serum Institute of India using *Novavax, Inc.*'s Matrix-M adjuvant technology. Meantime, over 3,000 miles away in Rwanda, *Novartis AG* recently reflected on its role in the fight against malaria for the past 25 years and the development of next-generation treatments.

The Swiss major launched Coartem (artemether/lumefantrine), the first fixed-dose artemisinin-based combination therapy (ACT) for malaria in 1999. To date, together with the World Health Organization (WHO), it has delivered more than a billion treatment courses of the ACT, including more than 450 million of a child-friendly formulation, with the majority supplied without profit.

In April, Novartis and partner Medicines for Malaria Venture announced positive data from the Phase II/III CALINA trial, which evaluated a new formulation of Coartem to treat the smallest babies (under 5kg) with acute uncomplicated malaria for whom there is no approved treatment. The data from the study, which was conducted in Burkina Faso, the Democratic Republic of the Congo (DRC), Kenya, Mali, Nigeria and Zambia, have been submitted for regulatory review.

The company has also recently started a Phase III trial on its lead candidate ganaplacide, in combination with a new formulation of lumefantrine, to treat adults and children with acute uncomplicated malaria and address emerging parasite resistance to ACTs. The trial will be conducted in 14 countries in sub-Saharan Africa and India and should be completed in 2025.

Caroline Boulton, Novartis's global head of malaria program, told In Vivo on a recent media trip to Rwanda that the difficulty of setting up a study in so many countries at 39 different sites was a considerable challenge "and we laugh about it as a team because my study managers are turning

greyer on a daily basis because you have to think of absolutely everything." Every individual country has its own clinical trial processes, ethics committees and health authority import licenses, "so it generally takes us a year to get approvals from the time we submit protocols to actually be able to initiate a trial. Once the sites are open, we can generally enroll patients very quickly."

Boulton wants to see harmonization of clinical trials on a pan-African level that could mirror what happens in Europe, "where the countries get together, they discuss a protocol, send the company questions and we respond." Other issues include ensuring whether sites have the right infrastructure and resources to actually conduct trials in the right way with properly trained staff and, if not, putting it in place, she added.

> *"It was literally just a shed, and hundreds and hundreds of patients suffering from malaria." - Caroline Boulton*

Another factor is the political unrest that regularly impacts sub-Saharan Africa, such as the recently thwarted coup attempt in the DRC. When such events occur, Boulton said "we try and speak to the trial team and check they are all okay and if can we help in any way." Often the response is that they are not sure, with people unavailable to leave their houses because of curfews but the "the investigators we work with feel that the show must go on and we'll find ways to make it work."

Getting sites onboard required innovative ways of working, she said, and an example of this is Novartis's partnership with the Swiss Tropical And Public Health Institute (TPH). "We were discussing with them that we needed some more clinical trial sites and as a result of our discussions, we saw there was a big untapped population down in the south of the DRC, in the Lubumbashi region. We were very keen to make a difference and improve the infrastructure there."

Some of Boulton's team went with colleagues from the TPH to have a look at the facilities in the Lubumbashi region and "it was literally just a shed, and hundreds and hundreds of patients suffering from malaria." The partners came up with a plan of action "where we would fly in a 'lab in a box,' a fully equipped shipping container that could be assembled on site and become a permanent health facility. It's all fixed up and ready to go and while it is going to help us run clinical trials, more importantly, it will there in the longer term to treat patients."

The lab in a box highlights the enormous undertaking involved and Boulton said "I think only somebody like Novartis with its size and scale can do it. We've got the ability to pull in different parts of the organization because it takes an army of people to get these studies up and running." In her previous roles, she was used to supervising "multiple thousands of patients in cardiovascular trials [and] that's a piece of cake compared to this."

Promising Pipeline

As well as ganaplacide, Novartis is also developing cipargamin which has a novel, fast-acting, long-lasting mechanism of action that is also potent against artemisinin-resistant Plasmodium strains. It is being evaluated in the KARISMA Phase II trial for severe malaria versus artesunate and versus Coartem.

Boulton was particularly excited about the Phase II platform trial called PLATINUM for uncomplicated Plasmodium falciparum malaria, which is looking at ganaplacide, cipargamin, Coartem and INE963, a fast acting long-lasting antimalarial with an entirely new mechanism of action. "It is a unique trial and while platform studies are run in the US and Europe, nobody's ever tried to do one in Africa," she said.

The premise "is a very interesting one as we have all these arms running in parallel and we choose the best combinations. We're even testing a triple combination and we'll see what it looks like. We know efficacy won't be a problem, but we have to look at safety as it's got to have the right benefit risk," Boulton added.

These are exciting times in the battle to eradicate malaria and the news from Côte d'Ivoire has attracted worldwide attention. R21 is the second malaria vaccine available in Africa following *GSK plc*'s Mosquirix and WHO expert reviews of data of the two products show that both vaccines are expected to have high public health impact, in conjunction with existing prevention methods such as the use of bed nets.

Novartis Measures Malaria Success On Impact Rather Than Money

By Kevin Grogan

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The Swiss major's global health chief Lutz Hegemann tells *Scrip* on a trip to Rwanda that being a profitable enterprise while helping to improve access to new and older therapies for those who need it most is the real measure of a successful business.

Read the full article here

> *"We have fallen behind WHO targets for reducing incidence and mortality globally." - Lutz Hegemann*

The efforts of Novartis, GSK, other pharma players and non-governmental organizations have made a considerable dent in the spread of one of world's most deadly diseases. Still, despite advancements that have led to a 35% reduction of malaria in the past 20 years, 249 million cases and 608,000 deaths occur worldwide each year and 95% of those deaths are in Africa.

In Rwanda, there was an 80% reduction in infection rates and an 89% decrease in malaria deaths between 2016 and 2022, thanks to coordinated efforts by the government, the WHO and other partners, Lutz Hegemann, Novartis president of global health and sustainability told journalists on the media trip to the country.

However, "despite – and perhaps even due to – this remarkable progress, Rwanda is one of four African countries where emerging signs of parasite resistance to artemisinin have been identified," he noted, "and we have fallen behind WHO targets for reducing incidence and mortality globally."

Climate change further complicates the issue with the rise in temperatures, excessive floods and heavy rainfall creating an ideal breeding grounds for mosquitoes. However, "our efforts won’t stop until elimination," Hegemann concluded, stressing that multi-stakeholder collaborations were the key.