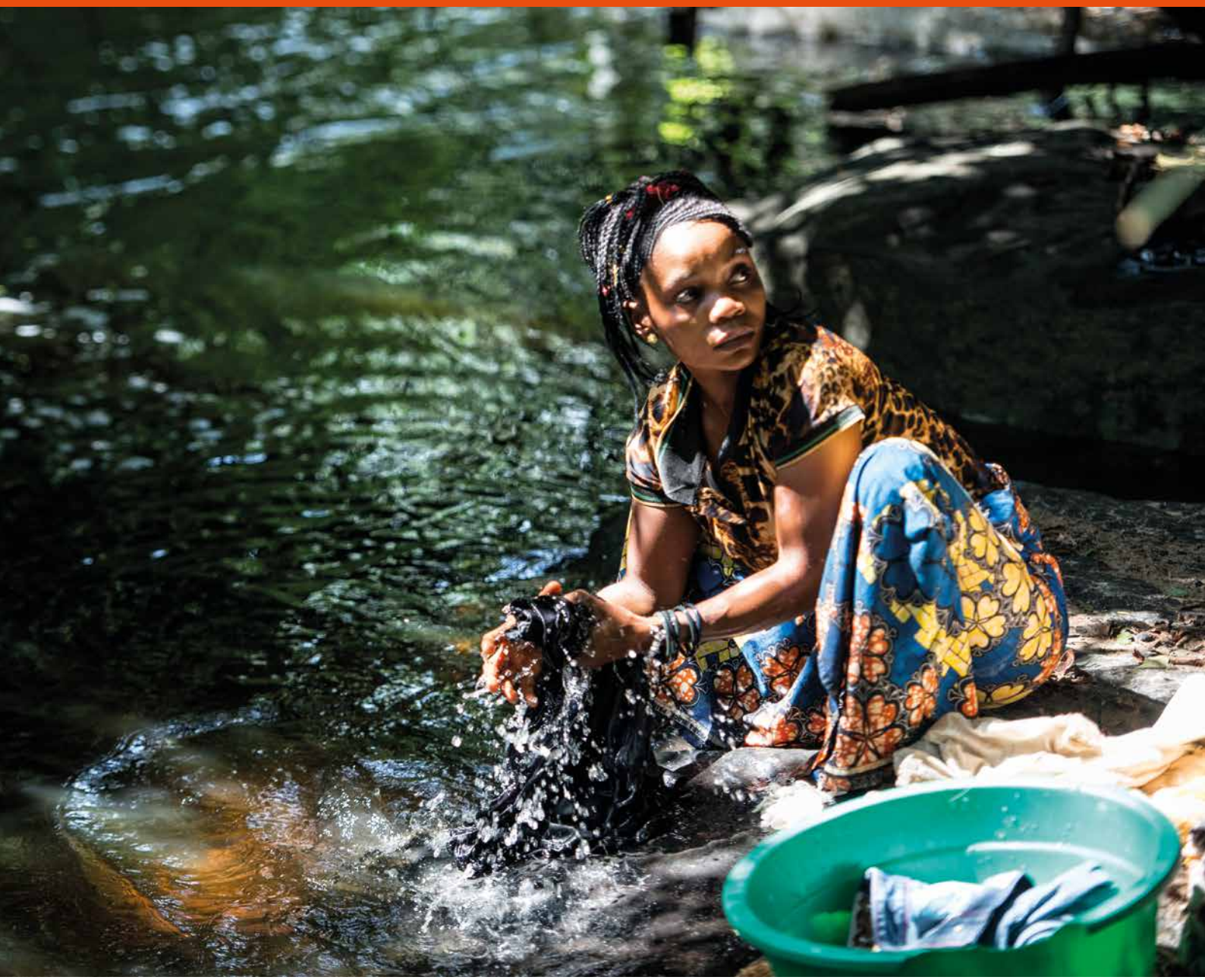
RIVER BLINDNESS: PUTTING PATIENT NEEDS FIRST



Developing a short-course treatment for onchocerciasis

DNDi
Drugs for Neglected Diseases *initiative*

> **“Sometimes I cry all night – my head hurts for lack of hope.”**
>
> Gertride Mapuani, 61, was kicked out of her house when she went blind after years of blackfly bites. Her neighbours support her now in the village of Babagulu, Democratic Republic of Congo.

Photo: Neil Brandvold/DND*i*

New treatments are needed for the millions of people in sub-Saharan Africa at risk of contracting onchocerciasis, also known as river blindness. Although the currently available treatment prevents infection and morbidity, patients need improved tools that offer a rapid cure for river blindness.

The current approach to river blindness is based on prevention through the mass administration of ivermectin donated by Merck and Co., Inc. and given to populations at risk of infection. While highly effective, these mass drug administration (MDA) programmes need to be repeated for 10-12 years or more, as current treatments only kill the juvenile filarial worms that cause river blindness, and adult worms can live more than 17 years in the human body. Moreover, ivermectin can cause apotentially fatal reaction in people infected by another filarial disease, *Loa loa*. For this reason, MDA programmes have been slowed down in co-endemic countries. Although MDA has been tremendously successful in many countries, in some regions patients are being left behind because of the lack of appropriate drugs to treat the disease.

DND*i* aims to develop a safe, effective, affordable, and field-adapted “macrofilaricidal” drug that can kill adult filarial worms and be used for individual patient treatment.

To respond to this unmet medical need, the Drugs for Neglected Diseases *initiative* (DND*i*) aims to develop a safe, effective, affordable, and field-adapted “macrofilaricidal” drug that can kill adult filarial worms and be used for individual patient treatment. DND*i*’s programme for onchocerciasis will contribute to efforts to control and eliminate this disease.

RIVER BLINDNESS: WHY ARE NEW TREATMENTS NEEDED?

River blindness is caused by *Onchocerca volvulus*, filarial nematode worms that are transmitted by the bite of an infected blackfly. Around 198 million people live in regions at risk of river blindness, as of 2016.[1] People are infected by repeated exposure to blackflies, which breed in fast-moving rivers. The flies transmit juvenile worms, or microfilariae, into the host, which can cause severe itching, disfiguring skin lesions, and impaired vision – all symptoms that cause immense suffering. Repeated infection causes eye disease that can lead to blindness.

Historically, onchocerciasis caused thousands upon thousands to go blind in Africa – entire communities would flee riverside areas in endemic regions to avoid the disease. The Onchocerciasis Control Programme (OCP) was launched by the World Health Organization (WHO) in the 1970s and was able to bring river blindness under control in West Africa, mostly through insecticide spraying. In 1995, the African Programme for Onchocerciasis Control (APOC) was launched, with its main strategy being community-directed treatment with the anti-parasitic drug ivermectin.

Historically, onchocerciasis caused thousands upon thousands to go blind in Africa – entire communities would flee riverside areas in endemic regions to avoid the disease.

Ivermectin is donated by Merck and Co., Inc through the Mectizan Donation Programme and distributed by thousands of unpaid volunteers through MDA programmes. It kills juvenile worms and is extremely effective and safe – it earned the Nobel Prize for medicine in 2015. The drug prevents infection by interrupting transmission of juvenile worms, and it also prevents blindness and skin disease associated with onchocerciasis.

APOC closed in 2015 and is widely considered to be one of the most successful public health programmes in history. In APOC's final year alone, more than 119 million people were treated with ivermectin.[2] After decades of ivermectin and other control efforts, many countries in Africa as well as in Asia and Latin America are reporting or will soon achieve elimination of onchocerciasis.

FACTS ABOUT RIVER BLINDNESS (ONCHOCERCIASIS)

17 million people are infected with river blindness

River blindness is the world's second-leading infectious cause of blindness

99% of infected people live in 31 African countries

1 World Health Organization (2017). Progress report on the elimination of human onchocerciasis, 2016–2017. *Wkly Epidemiol Rec.* 2017;92(45):681-700.

2 World Health Organization (2018). Fact sheet on onchocerciasis. Available at: http://www.who.int/en/news-room/fact-sheets/detail/onchocerciasis

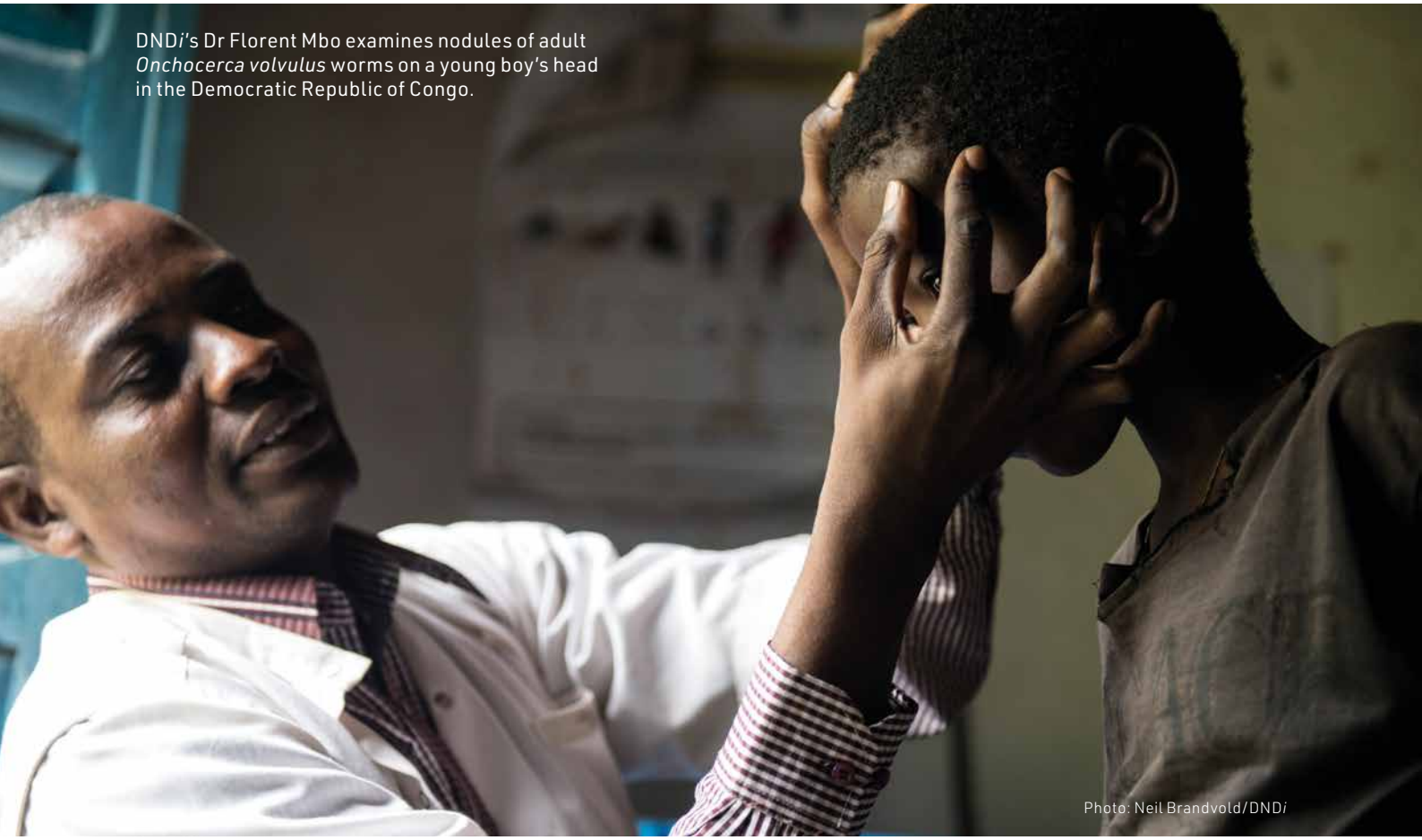
Yet some gaps remain. Since MDA must be repeated once or twice a year for many years until the adult worms die of natural causes, elimination of the disease with current tools will take many decades in heavily endemic areas. Furthermore, ivermectin can cause severe side effects for those infected with another filarial worm known as *Loa loa*, or African eye worm. Because of the risk of adverse effects, MDA programmes are not being carried out in some co-endemic areas in Central Africa. *Loa loa* affects over 10 million people in West and Central Africa.[3]

DND*i* is partnering with both Erasmus University, the Netherlands and Imperial College, UK to conduct epidemiological and mathematical modelling studies about the impact of ivermectin treatment, the future burden of the disease, and the projected number of people with onchocerciasis-*Loa loa* co-infection in order to better estimate the number of people that will need treatment in coming years, and the specific medical needs of patients.

New tools are needed for case management of patients and "mop-up" campaigns after MDA, and to support elimination goals using MDA strategies, namely a macrofilaricidal treatment that can kill the adult macrofilariae.[4]

What are the unmet medical needs for river blindness?

- Ivermectin, the drug used in MDA programmes, only kills juvenile worms and has to be given regularly
- Non-adherence in MDA programmes means that not everyone is reached
- Ivermectin is not registered for case management in endemic countries (for treating individual patients)
- Ivermectin cannot be safely used in areas co-endemic for river blindness and *Loa loa*.



DND*i*'s Dr Florent Mbo examines nodules of adult *Onchocerca volvulus* worms on a young boy's head in the Democratic Republic of Congo.

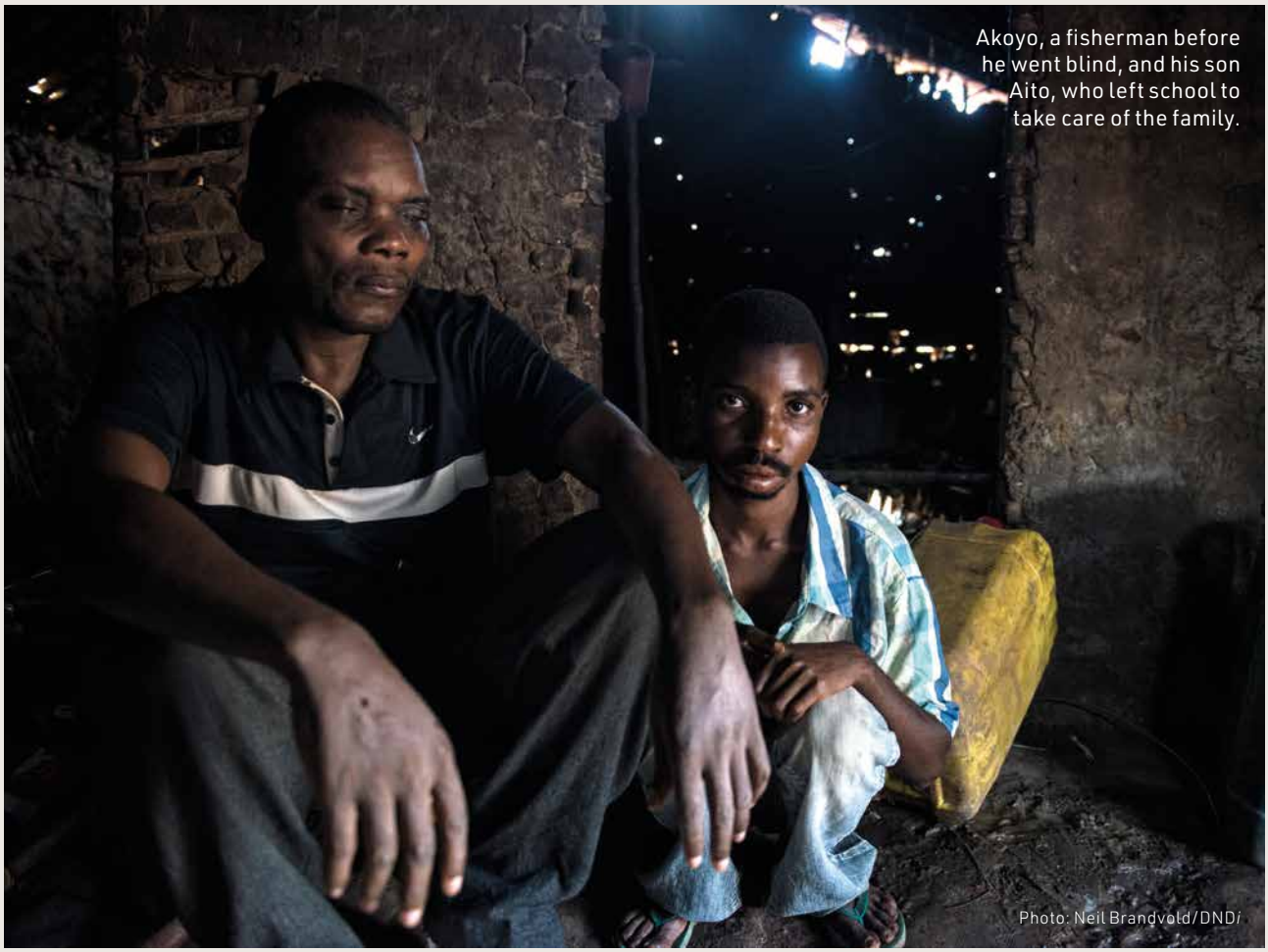
Photo: Neil Brandvold/DND*i*

3 Metzger WG Mordmüller B Loa loa–does it deserve to be neglected? *Lancet Infect Dis*. 2014; 14: 353-357 https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(13)70263-9/fulltext

4 In June 2018, the United States Food and Drug Administration (FDA) approved moxidectin as the first new river blindness treatment in 20 years, allowing this drug – which is not a microfilaricide – to be used in MDA. (See TDR (2018). First new treatment for river blindness approved by U.S. FDA in 20 years. TDR news item, 14 June 2018. Available at: http://www.who.int/tdr/news/2018/moxidectin-approved-as-treatment-for-river-blindness/en/)

"It went completely white"

A village consumed by river blindness



Akoyo, a fisherman before he went blind, and his son Aito, who left school to take care of the family.

Photo: Neil Brandvold/DNDi

Babagulu village in the Democratic Republic of Congo (DRC) is one of the many villages in the region devastated by river blindness. Thick equatorial jungle envelopes these villages, and the closer one gets to fast moving rivers, the more blind people one can find. Babagulu is split in two by the Onane River, and many villagers spend their lives by its banks. Local leaders estimate that up to 3% of the community is blind.

Akoyo was a fisherman like so many men in the community. But he also volunteered to distribute ivermectin and would go far into the bush to distribute the drug. He ended up missing many MDAs himself and eventually went blind. "It just went completely white," he remembers. Now Akoyo's son Aito has left school to take care of his family.

His story is not unique. Children and spouses give up their livelihoods to take care of blind people. In a region heavily endemic for *Loa loa*, Babagulu was also the site of some deaths due to adverse effects of ivermectin in 2003, and the scars are still evident. "People are scared to take the drugs – they are scared of side effects," says Anyasi, a community-directed distributor of ivermectin, pictured. "People don't understand why they have to take a drug that doesn't cure them as well, since they will still have the nodules even after taking medicines."

Local leaders estimate that up to 3% of the community is blind.

"People are scared to take the drugs – they are scared of side effects."

Anyasi (on the right) with volunteer drug distributors and a woman who has many nodules caused by the worms.

Photo: Neil Brandvold/DNDi

DND*i*'s drug development project portfolio

Three projects for onchocerciasis

DND*i* has a robust portfolio of three projects for onchocerciasis and is pursuing the clinical development of new additional drug candidates. DND*i* aims to complete Phase III studies and achieve registration of at least one new drug for river blindness.

EMODEPSIDE

DND*i* and Bayer Pharma are developing emodepside as a new macrofilaricidal treatment. Originating from the Japanese pharmaceutical company Astellas, emodepside was developed and is currently commercialized by Bayer Animal Health as a veterinary drug for cats and dogs. It has the potential to kill adult filarial worms quickly and could be used for case management.

DND*i* signed a collaboration agreement with Bayer in 2014 to jointly develop emodepside for the treatment of onchocerciasis in humans. DND*i* is responsible for clinical development and Bayer for pre-clinical and pharmaceutical development, as well as for manufacturing, registration, and market supply of the drug at the lowest sustainable price.

Emodepside has the potential to kill adult filarial worms quickly and could be used for case management.

First-in-human studies for emodepside in healthy volunteers are being finalized, with a single ascending dose study already completed and the multiple ascending dose study to be completed by the end of 2018.

As a next step, DND*i* plans to run a Phase II "proof-of-concept" clinical trial in sub-Saharan Africa, investigating the safety and efficacy of the drug in people living with onchocerciasis.

OXFENDAZOLE

Oxfendazole is currently under development for the treatment of neurocysticercosis and trichuriasis. Taking advantage of pre-clinical work already conducted by John Hopkins University, DND*i* is exploring the possibility of repurposing oxfendazole as a macrofilaricidal treatment for filarial indications. DND*i* intends to initiate a first-in-human trial and complete formulation development.

ABBV-4083 (TYLAMAC®)

ABBV-4083 (TylAMac®) is a derivative of Tylosin, a veterinary antibiotic, and is being developed by DND*i* and AbbVie as a potential macrofilaricidal drug. ABBV-4083 targets the *Wolbachia* bacteria that have an endosymbiotic relationship with the worms that cause river blindness. Targeting the *Wolbachia* bacteria kills the worms gradually over a long period of time, which results in fewer side effects for treated patients. Because *Loa loa* do not have *Wolbachia*, an antibiotic like TylAMac® could be given safely in co-endemic *Loa loa*-onchocerciasis areas.

ABBV-4083 is orally available and induces a robust anti-*Wolbachia* effect in several *in vivo* models. It demonstrates clear superiority over doxycycline, another antibiotic investigated for filarial diseases. It is effective with a shorter dosing regimen, and preliminary safety and toxicology profiling of this compound suggests a favourable safety profile.

The first in human trial is taking place at AbbVie's Clinical Pharmacology Research Unit.

DND*i* plans to run a "proof-of-concept" clinical trial in sub-Saharan Africa, testing the drug in people living with onchocerciasis.

ABBV-4083 targets the *Wolbachia* bacteria that have an endosymbiotic relationship with the worms that cause river blindness.

Skin lesions caused by onchocerciasis, known as "leopard skin".

Photo: Neil Brandvold/DND*i*

DND*i*'s drug discovery programme

New drug candidates for onchocerciasis

Photo: DK Lee/DND*i*

SCREENING

DND*i*'s filarial disease programme actively identifies potential new drug candidates for onchocerciasis by evaluating registered drugs, as well as pre-clinical and clinical drug candidates. DND*i* also investigates chemical compounds with known activity against filarial worms.

Well-characterized libraries of compounds that had already been extensively optimized for other indications were provided to DND*i* by several pharmaceutical companies for screening. Some 530 compounds have now been screened in partnership with Salvensis, Merck Sharp & Dohme, University of Carolina, AbbVie, and others. From this initial screen, a full lead optimization programme to further develop these compounds has been undertaken in collaboration with Celgene, with additional exploration of identified "hits". This effort will continue, with the aim of delivering several back-up drug candidates for filarial diseases.

BIOMARKERS

As part of its drug development programme for onchocerciasis, DND*i* is identifying surrogate markers (biological or non-biological) that correlate with filarial worm levels in the human body to measure treatment effectiveness, and for the future development of better, field-adapted diagnostic methods. This includes:

- Imaging Technique Diffuse Reflectance Spectroscopy (DRSsr): A non-invasive, light-based detection device to identify live and dead parasites in the patient's subcutaneous nodules.
- A serological biomarker to identify *O. volvulus* peptides in urine and serum samples from onchocerciasis patients, with the aim of developing a rapid diagnostic test to determine the presence of onchocerciasis infection and to assess treatment success.
- Genotyping of *O. volvulus* parasites to tell the difference between treatment failure and re-infection.

Thank you

Thank you to our partners and donors for the onchocerciasis programme

DNDi PARTNERS

- AbbVie, USA
- AWOL, UK
- Analytical Services International, UK
- Bayer, Germany
- Bonn University Hospital, Institute of Medical Microbiology, Immunology and Parasitology, Germany
- Celgene Corporation, USA
- Hammersmith Medicines Research, UK
- Imperial College, UK
- Institut Bouisson Bertrand, France
- Liverpool School of Tropical Medicine, UK
- Mahidol University, Thailand
- Merck, USA
- National Museum of Natural History, France
- Niche Science and Technology, UK
- Northwick Park Institute for Medical Research, UK
- Salvensis, UK
- University of Carolina, USA
- University of Health and Allied Sciences, Ghana
- University of Washington, USA
- Erasmus MC University, the Netherlands
- CEA-LETI, Grenoble, France
- REFOTDE, Buea, Cameroon

THANK YOU TO OUR DONORS

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SPONSORED BY THE Federal Ministry of Education and Research through KFW

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Confédération suisse
Confederazione Svizzera
Confederaziun svizra

And with the support of the Brian Mercer Charitable Trust

“You’ve got to help people, you can’t leave people like this.”

Angel Mozenge is a volunteer drug distributor from the village of Uma, DR Congo. She thinks that over half of the population of her village refuses to take the MDA drug.

Photo: Neil Brandvold/DNDi

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A not-for-profit research and development organization, DND*i* works to deliver new treatments for neglected diseases, notably leishmaniasis, human African trypanosomiasis, Chagas disease, specific filarial infections, and mycetoma, and for neglected patients, particularly those living with paediatric HIV and hepatitis C.

Since its inception in 2003, DND*i* has delivered eight treatments: two fixed-dose antimalarials (ASAQ and ASMQ), nifurtimox-eflornithine combination therapy (NECT) for late-stage sleeping sickness, sodium stibogluconate and paromomycin (SSG&PM) combination therapy for visceral leishmaniasis in Africa, a set of combination therapies for visceral leishmaniasis in Asia, paediatric dosage forms of benznidazole for Chagas disease, a 'super-booster' therapy for children co-infected with HIV and TB, and the first all-oral drug for sleeping sickness (fexinidazole).

Cover image: Regine Bora, 20, washes her clothes in the Onane River on the outskirts of Babagulu. She refuses to take MDA medicines because of fear of side effects. Photo: Neil Brandvold/DND*i*.

This report is made possible by the generous support of the American people through the United States Agency for International Development (USAID). The contents are the responsibility of the Drugs for Neglected Diseases *initiative* and do not necessarily reflect the views of USAID or the United States Government.