LEISHMANIASIS

Delivering safer, simpler treatments to save lives and reduce social stigma

FACTS

Over 1 billion

people at risk of leishmaniasis worldwide

Over 600 thousand

new cases of CL every year

About 50%

of people with leishmaniasis are children

Caused by parasites transmitted through the bite of a sandfly, leishmaniasis has strong links to poverty, taking its heaviest toll on people affected by malnutrition, poor housing, and displacement.

Visceral leishmaniasis (VL) – also known as kala-azar – is the second deadliest parasitic disease after malaria and causes fever, weight loss, spleen and liver enlargement, and, if not treated, death. **Cutaneous leishmaniasis (CL)** leaves lifelong scars, including on the face, causing social stigma, particularly for women and children. **Post-kala-azar dermal leishmaniasis (PKDL)**, a complication of VL, appears as a rash or skin condition months or years after successful VL treatment and may act as a reservoir for VL infection. Although CL and PKDL are not deadly, they can be highly stigmatizing.

Leishmaniasis treatment depends on several factors, including the form of the disease, parasite species, and geographic location. For decades, treatments have required long hospital stays and painful injections of toxic antimonial drugs, such as sodium stibogluconate (SSG).

The push for progress

Together with our partners, DNDi has delivered four safer, simpler treatments for VL and PKDL – and we are making major strides towards our longer-term goal: developing all-new drugs that can revolutionize treatment and help boost global efforts to eliminate the disease. We have established two research networks that are central to these advances. Founded in 2003, the Leishmaniasis East Africa Platform (LEAP) includes 60 experts from 20 institutions who have helped drive progress in Kenya, Ethiopia, Uganda, South Sudan, and Sudan. Established in 2014, redeLEISH is a global network of CL experts working across 90 institutions in 28 countries sharing know-how and designing and conducting vital clinical research.

OUR GOAL IS NOW to continue implementing safer, shorter treatments with existing drugs while advancing the development of all-new treatments that can be delivered in primary healthcare settings, closer to affected communities. Ultimately, we aim to help reduce the burden of all forms of leishmaniasis and eliminate VL as a public health problem in all affected regions.

An improved treatment for children and adults in Eastern Africa

Safer, simpler, shorter treatments for VL in Eastern Africa are urgently needed – especially for children, who comprise up to 70% of cases in the region.

> “This disease took away my will to live.

NAND, from Balwan Tola in Bihar, India, has had visceral leishmaniasis four times. As his health declined, so did his income, and he became more isolated in his community. Even worse, his son was also infected. Luckily, they were both able to receive treatment. Without it, visceral leishmaniasis is 95% fatal.

DNDi and partners conducted a Phase III study in Ethiopia, Kenya, Sudan, and Uganda to compare the combination of miltefosine and paromomycin (MF+PM) against the standard treatment, SSG+PM. Results published in 2022 showed that MF+PM was as effective as SSG+PM but with fewer injections, a shorter treatment duration, no risk of SSG-related toxicity, and a decreased risk of subsequent PKDL. Results from our follow-on population pharmacokinetics study published in 2023 showed adequate paediatric exposure of MF+PM in children – reinforcing the evidence to support implementation of the shorter, less painful treatment regimen for both children and adults.

Following a review of the evidence from DNDi’s Phase III trial, the WHO Guideline Development Group (GDG) is expected to release new treatment guidelines in 2025 that pave the way for implementing MF+PM as a safer, simpler standard of care for adults and children with VL in Eastern Africa. Combined with vector control and improved access to diagnosis and treatment, the improved regimen may play a crucial role in reaching elimination goals in the region.

PKDL: two new treatments to break the cycle of infection

PKDL can act as a reservoir for VL infection, which makes early and effective PKDL treatment critical to achieving sustained reductions in VL transmission.

DNDi and partners conducted two Phase II studies for PKDL: one testing liposomal amphotericin B and miltefosine (LAmB+MF) and MF+PM in Sudan, and one testing LAmB monotherapy and LAmB+MF in India and Bangladesh. Findings from Sudan were published in the journal *PLOS Neglected Tropical Diseases* in November 2023, and findings from South Asia were published in the same journal in June 2024.

Evidence from both trials was included in a review by the WHO GDG, which sought alternative shorter, safer treatments for PKDL to replace the current 60- to 90-day antimonial treatment in Eastern Africa and 12-week miltefosine monotherapy treatment in South Asia. WHO is expected to recommend new treatments based on evidence from our trials in Bangladesh, Sudan, and India in its forthcoming updated treatment guidelines.

Breaking the barriers to elimination

By delivering safer, shorter treatments utilizing existing drugs, DNDi and partners have helped equip doctors and patients with life-saving alternatives to decades-old toxic antimonials. **But continued innovation is critical. New oral, safe, patient-friendly treatments are essential to achieving and sustaining leishmaniasis elimination in South Asia and Eastern Africa** (see page 8) – and will be crucial to integrating patient care at the primary healthcare level, countering future outbreaks, and fully meeting the needs of people with VL, PKDL, and VL/HIV.

DNDi has been working to develop all-new, all-oral treatments for leishmaniasis since our founding in 2003. Together with our partners, we have screened hundreds of thousands of compounds, evaluated promising leads, and optimized these into promising drug candidates.

One front-running candidate is LXE408, under development in partnership with Novartis. After a Phase I study completed by Novartis showed good tolerability and exposure, the first-in-class compound progressed to a Phase II study in India in 2022. Recruitment for a parallel Phase II study of LXE408 in Ethiopia kicked off in April 2024. Approximately 150 participants, including adolescents, are expected to be enrolled across the two trials by 2025, with studies completing by the end of the year.

Preparations for a Phase I study of another leading candidate – DNDI-6899 – also progressed in 2024 in partnership with the GSK Global Health Unit, the Drug Discovery Unit at the University of Dundee, University of Antwerp, and Wellcome. The Phase I study is expected to begin in early 2025 at the Royal Liverpool University, UK, in partnership with the University of Liverpool and the Liverpool University Hospitals NHS Foundation Trust. The project was recognized as a 2024 Project of the Year by the DNDi Scientific Advisory Committee for outstanding progress in pre-clinical research.

With a new mode of action among compounds in DNDi's leishmaniasis portfolio, DNDI-6174 also has a predicted low human dose and a promising safety margin. DNDi and Eisai Co., Ltd. have collaborated on developing the compound since its nomination as a pre-clinical candidate in 2019. DNDi completed pre-clinical development of DNDI-6174 and selected it as a clinical candidate in 2024, with results from pivotal 28-day toxicity studies supporting its progression to Phase I studies and reinforcing evidence of the compound's excellent pharmacological profile.

CUTANEOUS LEISHMANIASIS

Shorter, safer, more effective treatments to replace toxic antimonials

For nearly 70 years, treatments for cutaneous leishmaniasis (CL) have been costly and have often required weeks of painful injections of toxic antimonials. A Phase II study conducted by DNDi and partners showed that a combination of thermotherapy – where heat is applied to a person's lesions – and a shorter course of miltefosine yielded better outcomes than thermotherapy alone in treating uncomplicated CL in the Americas.

Based on these results, we conducted a Phase III study at six sites in Bolivia, Brazil, Panama, Peru. The last patient visit was completed in January 2024 – with a total of 127 patients enrolled: 64 in the miltefosine monotherapy arm and 63 in the miltefosine + thermotherapy arm. Study results showed that the combination treatment was as effective as miltefosine alone and, importantly, more effective for lesions caused by *L. braziliensis* – the most common cause of CL in the Americas.

> "People keep asking me what happened to my face and why the scar is not going away. I don't have an answer for them.

ABDELLA is an 18-year-old living with cutaneous leishmaniasis in southern Ethiopia. The lesion on his forehead started with what looked like a small acne pimple but continued to grow larger as the months went by. After trying several treatments with no result, he met a friend who had a similar lesion and had been treated at the ALERT hospital in Addis Ababa, where Abdella resumed his treatment journey.

Boosting access to thermotherapy

Despite being a practical and effective treatment option for uncomplicated CL, thermotherapy has long been very difficult to access, especially in remote areas. In 2024, DNDi joined with the Pan-American Health Organization (PAHO) and partners in the redeLEISH network to expand access to thermotherapy, supporting the provision of 16 thermotherapy machines through donations and training of health workers in seven countries.

A potential all-new treatment for CL

Alongside our evaluation of the safety and efficacy of LXE408 for the treatment of VL in two ongoing Phase II studies in India and Ethiopia – and following promising pre-clinical research that showed the compound's potent anti-parasitic activity against the parasites that cause CL – DNDi, Novartis, and partners are now exploring its potential as a treatment for CL in the Americas. Preparations for a Phase II trial testing the safety and efficacy of two oral regimens of LXE408 compared with oral miltefosine got underway in 2024, with patient recruitment expected to commence in late 2025.