DNDi
Best Science for the Most Neglected

DISEASE FACTSHEET

LEISHMANIASIS

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

Caused by parasites transmitted through the bite of a sandfly, leishmaniasis is a climate-sensitive disease that takes its heaviest toll on people affected by poverty, 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 disfiguring and 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, heavy-metal-based antimonial drugs, such as sodium stibogluconate (SSG).

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

» THE PUSH FOR PROGRESS

Together with our partners, DNDi has delivered four safer, simpler treatments for VL and VL/HIV co-infection – 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 endemic country-led research networks that are powering progress against the disease. Founded in 2003, the Leishmaniasis East Africa Platform (LEAP) includes 60 experts from 20 institutions who are helping drive progress in Kenya, Ethiopia, Uganda, South Sudan, and Sudan. Established in 2014, redeLEISH is a global network of CL experts working across 91 institutions in 28 countries who share know-how and design and conduct 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. With better treatments, we aim to help reduce the burden of all forms of leishmaniasis and ultimately eliminate VL as a public health problem in affected regions.

A PIVOTAL MOMENT IN THE FIGHT AGAINST VISCERAL LEISHMANIASIS

For decades, leishmaniasis treatment was defined by painful, toxic drugs that required weeks of hospitalization and disrupted lives already strained by poverty, insecurity, and limited access to healthcare. Now, sustained innovation, hard-won evidence, strong partnerships, and political commitment are beginning to reshape how the disease is treated, controlled, and ultimately eliminated. **At the core of these advances is a simple belief: treatments must be adapted to patients' needs, simple and safe to use, and accessible to affected communities.**

> When I was diagnosed with kala-azar, I became too weak to continue going to school. I still wish I had completed my education and found a job so I could help support my family.

MADHURI lives in the small town of Garkha in Bihar, India. She was first diagnosed with kala-azar in 2017 and later with PKDL. Illness and financial strain forced her to leave school; she now works in the fields to support her family.

Photo credit: JDot-DNDi

As the front-running candidate in DNDi's leishmaniasis portfolio, LXE408 offers new hope for a long-held ambition: to deliver a short-course, oral treatment that can be used at the primary healthcare level. LXE408 is a first-in-class oral compound active against multiple Leishmania species developed in partnership with Novartis. All study visits for the two Phase II proof-of-concept studies for VL were completed in 2025, with early results showing good efficacy and safety. Full results are expected to be released in 2026, and planning for a pivotal Phase III trial for VL in Eastern Africa is now underway.

While LXE408 shows significant promise, the reality remains that a single drug is unlikely to meet the treatment needs of all patients, including patients affected by certain parasite species. DNDi's balanced and robust portfolio intentionally reflects this reality, with two further oral compounds – DNDI-6899 and DNDI-6174 – in clinical development.

Designed for combination use to preserve the long term goals of our leishmaniasis programme, DNDI-6899 is the second most advanced candidate, progressing towards studies in patients. Developed through a collaboration between the GSK Global Health Unit and the Drug Discovery Unit at the University of Dundee, DNDI-6899 entered Phase I food effect and multiple ascending dose studies in April 2025 at the Royal Liverpool University, UK, in partnership with the University of Liverpool and the Liverpool University Hospitals NHS Foundation Trust. The trial is expected to conclude in 2026, and its results will determine whether DNDI-6899 is suitable for later trials in patients with VL, with a primary focus on Africa, and for potential clinical development for patients with CL, as well.

With a new mode of action among compounds in DNDi's leishmaniasis portfolio, DNDI-6174 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. A formal Scientific Advice Meeting with the Medicines and Healthcare products Regulatory Agency in 2025 determined that the available pre-clinical data supported the planned first-in-human trial and that the study design was acceptable. Phase I studies are expected to begin in 2027.

DELIVERING BETTER TREATMENTS NOW FOR THOSE MOST AT RISK

Science only delivers impact when it changes practice to improve lives and protect livelihoods. **Years of research into improving treatments with existing drugs will soon bear fruit in new treatment guidelines for VL in Eastern Africa and PKDL in Eastern Africa and South Asia to be issued by the World Health Organization (WHO).** More than a technical update, the new guidelines will send a clear signal that cures for leishmaniasis must move beyond toxic, painful antimonial injections and long hospital stays, ambitions which have been the mainstay of the DNDi strategy for leishmaniasis R&D since our founding.

The forthcoming combination treatment of oral miltefosine (MF) and the injectable antibiotic paromomycin (PM) for VL in Eastern Africa was developed following clinical trials in Ethiopia, Kenya, Sudan, and Uganda conducted by DNDi and partners, including members of the AfriKADIA consortium. **Results showed MF+PM was as effective as SSG+PM – the current standard of care in Eastern Africa – for children and adults, but with fewer injections, a shorter treatment duration, no risk of SSG-related toxicity, and a decreased risk of subsequent PKDL.**

The forthcoming combination treatments MF+PM and liposomal amphotericin B (LAmB)+MF for the treatment of PKDL in Eastern Africa were evaluated by DNDi and the Institute of Endemic Diseases, Khartoum University in Sudan, where nearly 20% of former VL patients develop PKDL – the highest rate in the world. Results showed that the combinations achieved a satisfactory cure rate against PKDL with a much shorter hospitalization period of 7 or 14 days compared to 60-90 days for the previous treatment based on SSG injections.

In South Asia, PKDL contributes to perpetuating the VL transmission cycle and could undermine hard-won progress towards elimination. The current treatment for PKDL in South Asia is based on long administrations of MF, which are associated with low adherence and risks such as ocular toxicity. A study conducted by DNDi and partners in India and Bangladesh confirmed that LAmB as monotherapy or in combination with a short three-week course of MF achieves cure rates similar to previous regimens while reducing overall treatment duration and associated risks. **We anticipate that these and other results will be reflected in new WHO guidelines recommending LAmB as monotherapy or in combination with MF for the treatment of PKDL in South Asia.**

CUTANEOUS LEISHMANIASIS

Current treatments for cutaneous leishmaniasis (CL) have been in use for more than 70 years. Patients – many of them children – still endure weeks of painful injections with toxic antimonial drugs for a disease that can leave lifelong scars and cause severe social stigma.

DNDi's strategy for CL recognizes the need to move away from one-size-fits-all treatment approaches and towards regimens tailored to disease severity, causative parasite species, and specific healthcare settings. For uncomplicated CL, this means reducing or eliminating systemic exposure as much as possible in favour of topical and localized therapies. For patients requiring systemic treatment, it means developing simpler oral therapies that can replace painful and often unsafe treatments, as well as treatments that address the needs of patients with complicated forms of CL that do not respond to oral therapies.

TURNING THE CORNER IN NEW TREATMENT RESEARCH

Following promising pre-clinical research showing LXE408 to have potent activity against the parasites that cause CL, DNDi, Novartis, and partners are preparing for a Phase II study evaluating the compound against

> I would prefer treatment with pills instead of injections.

LUIS EDUARDO, a miner from Remedios, Colombia, developed mucosal leishmaniasis – a severe complication of cutaneous leishmaniasis. It caused painful nasal lesions that forced him to sleep upright for seven months and made it difficult for him to work.

Photo credit: Sydelle Willow Smith-DNDi

CL in the Americas, set to begin in 2026. **This first clinical trial of a new chemical entity for CL signals renewed commitment to innovation for shorter, better-tolerated treatments for a disease long sidelined in drug development.**

In partnership with Ajinomoto Bio-Pharma Services (GeneDesign, Inc.) and the University of Tokyo, our teams have also continued work to advance development of CpG-D35 (DNDI-2319), an immunomodulator designed to stimulate the immune system to fight infection. For use in combination with drug therapy for complicated forms of CL, we aim to meet the needs of patients with multiple or large lesions, facial lesions, prior treatment failure, or diffuse and disseminated forms of CL. Preparations are underway for a new sequential study of CpG-D35, consisting of a multiple-ascending-dose study followed by a proof-of-concept trial. The study synopsis was reviewed and endorsed by both SwissMedic and the World Health Organization in 2025.

SAFER, SIMPLER, MORE ACCESSIBLE TREATMENTS FOR UNCOMPLICATED CL

Thermotherapy – where controlled heat is applied directly to lesions – offers a practical, effective option for uncomplicated CL with small lesions, avoiding systemic toxicity altogether. For years, access to the simple but effective treatment has remained limited, particularly in remote settings.

In partnership with the Pan American Health Organization (PAHO) and the redeLEISH network, DNDi has worked to expand access to thermotherapy across the Americas, supporting the provision of equipment and training healthcare workers in its use.

In Sri Lanka, DNDi provided technical advice and thermotherapy devices for a clinical trial testing the treatment against CL caused by *L. donovani*. In Ethiopia, a separate study testing the effectiveness of thermotherapy against CL caused by *L. aethiopica* was completed in 2025, with publication of results expected in 2026.