FACTS

LEISHMANIASIS

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

Over 600 million people at risk of VL worldwide

Over 600 thousand new cases of CL every year

About 50% of people with VL 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. 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.

The push for progress

With our partners, DNDi has to date delivered four improved VL treatments that have replaced more toxic treatments requiring long hospitalization. Through our long-term strategy, we have replenished the R&D pipeline with an unprecedented portfolio of all-new potential drugs that could revolutionize treatment and accelerate progress towards global elimination goals. The Leishmaniasis East Africa Platform (LEAP), founded by DNDi in 2003, includes 60 experts from 20 institutions who have helped drive progress against the disease in Kenya, Ethiopia, Uganda, and Sudan. In 2014, we established redeLEISH, a network of CL experts working across 90 institutions in 28 countries to share know-how and to design and conduct vital clinical research.

Our goal is now to achieve our final short-term ambitions in delivering safer, shorter treatments with existing drugs, while completing the longer-term development of all-new drugs to save lives, reduce social stigma, and eliminate leishmaniasis as a public health problem.

An improved standard of care for children and adults in Eastern Africa

Safer, simpler alternatives to the current standard treatment for VL in Eastern Africa are urgently needed – especially for children, who comprise up to 70% of cases. DNDi partnered with the AfriKADIA consortium to launch a Phase III study in Ethiopia, Kenya, Sudan, and Uganda in 2018 to compare the combination of miltefosine and paromomycin (MF+PM) against the current standard treatment, sodium stibogluconate and paromomycin (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 post-kala-azar dermal leishmaniasis (PKDL).

DNDi
Best Science for the Most Neglected

Photo credit: Lameck Ododo-DNDi

“She was so young back then. If there was a simpler treatment instead of injections, that would have made the experience much better – but I know that day is coming.

Selena (right) chats with her daughter, **Tegla,** and grandchildren at their home in the village of Lopedot in Amudat District, Uganda. Tegla was diagnosed with visceral leishmaniasis at a very young age. After unsuccessful treatment, Selena took Tegla to Amudat Hospital, where she received the right medication and was cured. Selena hopes that treatment will become easier – especially for children.

Ensuring adequate paediatric exposure to MF+PM is crucial for combatting VL in the region and providing better care to the most vulnerable. In September 2023, the results of DNDi and partners' follow-on population pharmacokinetics study published in the *Journal of Antimicrobial Therapy* confirmed that exposure levels of MF and PM were within the desired parameters in both patients ⩽12 years old and patients >12 years old, supporting implementation of the shorter 14-day regimen in both paediatric and adult patients.

DNDi disseminated the trial results to experts at the 7th World Congress on Leishmaniasis and 28th LEAP Platform meeting, as well as to leishmaniasis technical and advisory groups in the region and communities where the studies were conducted. At the same time, the WHO Guideline Development Group began reviewing the evidence generated in DNDi's Phase III trial to inform revised treatment guidelines for adults and children with VL in Eastern Africa.

PKDL: Breaking the cycle of infection

PKDL is a complication of VL that appears as a rash or skin condition months or years after successful VL treatment. Although it is not deadly, it can be highly stigmatizing. Because PKDL can act as a reservoir for VL infection, early and effective PKDL treatment is critical to achieving sustained reductions in VL transmission.

DNDi completed two Phase II studies in 2021, one testing liposomal amphotericin B (LAmB)+MF and MF+PM in Sudan, and one testing LAmB monotherapy and LAmB+MF in India and Bangladesh. Findings from the Phase II trial in Sudan were published in the journal *PLOS Neglected Tropical Diseases* in November 2023, and findings from the Phase II trial in South Asia were published in the same journal in June 2024. With both trials bringing evidence for shorter, safer

treatments to replace the current 60- to 90-day antimonial treatment in Sudan and 12-week miltefosine monotherapy treatment in South Asia, it is expected these alternative therapies will be recommended for patients with PKDL.

Pursuing the promise of all-new, all-oral drugs

By delivering safer, shorter treatments utilizing existing drugs, DNDi and our partners have helped equip doctors and patients with life-saving alternatives to decades-old toxic antimonials. Together with vector control and other community health efforts spearheaded by health authorities, the improved treatments have contributed to the tremendous strides made by countries in South Asia towards the elimination of leishmaniasis as a public health problem. **But continued innovation remains critical** (see page 10). **New drugs and drug combinations are needed to sustain elimination in South Asia and achieve it in eastern Africa** – and will also be essential to countering future outbreaks, and fully meeting the needs of patients with VL, PKDL, and VL/HIV coinfection.

DNDi has been working on developing 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 that can enter the drug development process.

In 2023, our teams and partners made significant advances in the development of new molecular entities that have the potential to revolutionize leishmaniasis treatment and support elimination of the disease as a public health problem.

DNDi is collaborating with Novartis on the joint development of LXE408, a first-in-class compound. Following results from a Novartis Phase I study completed in 2021 that showed good tolerability and exposure, the compound progressed to a Phase II study in India in late 2022. A second site for the study in India was initiated in August 2023, with 39 patients enrolled by the end of the year. In parallel, institutional ethics committee and regulatory approvals were obtained for a similar Phase II study in Ethiopia, with the first patient enrolled in April 2024. A total of 140 participants are expected to be enrolled across the two studies by 2025.

With a similar mode of action to LXE408, the compound GSK245 was developed through a collaboration between DNDi, GSK Global Health Unit, and the Drug Discovery Unit at the University of Dundee. After further investigations into the pharmacokinetics of the compound were completed, the development of GSK245 continued in 2023 with the completion of a Phase I single ascending dose study in healthy volunteers sponsored by GSK.

Following a scientific meeting with the UK Medicines and Healthcare Products Regulatory Agency in early 2023, DNDi and partners also resumed development of DNDI-6899 because of its unique mode of action demonstrated by the University of Dundee. The active pharmaceutical ingredient stored at WuXi AppTech was successfully reprocessed and formulated to support the initiation of a Phase I multiple ascending dose study in 2024.

DNDI-6174 presents a new mode of action among compounds in DNDi's leishmaniasis portfolio, as well as a predicted low human dose and a promising safety margin. Collaborating on the development of DNDI-6174 since its nomination as a drug candidate in 2019, DNDi and Eisai Co., Ltd. worked in 2023 to extend our knowledge of the compound's non-clinical profile with the goal of progressing to a first-in-human clinical trial. The outcomes of DNDi's previous work together with GSK and the University of Dundee on the discovery of DNDI-6174 that led to its nomination as a drug candidate for VL were published in *Science Translational Medicine* in December 2023.

The development of DNDI-6148 and DNDI-0690 remained on hold in 2023 in favour of the other promising compounds above.

CUTANEOUS LEISHMANIASIS

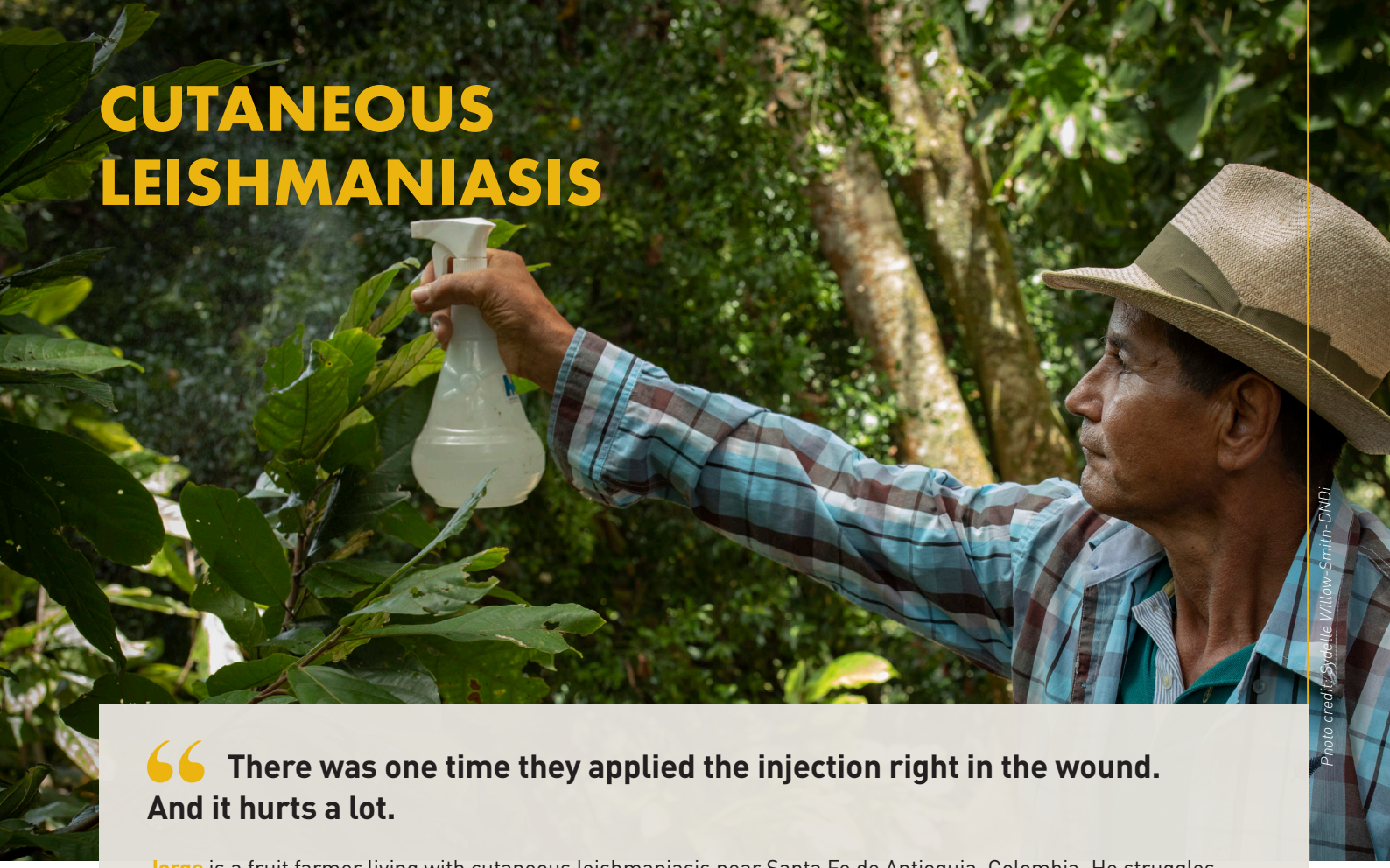

Photo credit: Sydelle Willow-Smith-DNDi

“There was one time they applied the injection right in the wound. And it hurts a lot.

Jorge is a fruit farmer living with cutaneous leishmaniasis near Santa Fe de Antioquia, Colombia. He struggles to access medical care, living outside of a major urban area, and has to travel long distances to reach his treatment centre.

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. In 2019, DNDi conducted a Phase II study showing that a combination of thermotherapy – where heat is applied to a person's lesions – and a short course of miltefosine yielded better outcomes than thermotherapy alone in treating uncomplicated CL in the Americas.

Based on results from our Phase II study, we initiated a Phase III study at four sites in Brazil, Panama, and Peru in 2021, and at a fifth site in Bolivia in 2022. The last patient visit in the trial was completed in January 2024 – with a total of 182 patients enrolled across the treatment arms. Final study results are expected in late 2024.

Stimulating the immune system's response to fight infection

Leishmania parasites can persist in human cells by evading or exploiting immune mechanisms. Together with our partners Ajinomoto Bio-Pharma Services (GeneDesign, Inc.) and the University of Tokyo, our teams are developing CpG-D35 (DNDI-2319) as a therapeutic 'booster' to promote the immune system's response against the parasitic infection that causes CL and improve the efficacy of existing drugs. DNDi is also exploring CpG-D35 for the important role it could play in preventing PKDL following VL infection.

DNDi completed a Phase I single ascending dose study in 2021. Results analysed in 2022 showed CpG-D35 to be safe and well tolerated after a single subcutaneous dose and supported advancement to a Phase I multiple ascending dose study in patients with uncomplicated CL, now underway in Colombia. Anticipating CpG-D35 use under real-life conditions, a more convenient, field-adapted lyophilized formulation of CpG-D35 was developed. Plans to assess this formulation in a Phase I multiple ascending dose study are ongoing.