Leishmaniasis: 98 countries, 1 billion people at risk

- Leishmaniasis is a complex vector-borne disease with different clinical manifestations:
  - Primary targets for the programme: VL and CL.
  - Secondary targets: PKDL, HIV-VL, complicated CL.
- Linked to environmental changes such as deforestation, building of dams, irrigation schemes and urbanization*.
- Affects some of the poorest people on earth*.
- Prone to outbreaks, mainly related to displacement of vulnerable population due to conflict.
- 700,000 to 1.4 million new cases occur annually*; 14,454 deaths associated with leishmaniasis

*WHO, 2020
Cutaneous Leishmaniasis

- Endemic in **88 countries**
- 0.7 to 1.2 million new CL cases annually worldwide.
- Every **30 seconds** there is a new case of CL
- Eastern Mediterranean region contribute to ~60% of global CL burden

- >12 species and dozens of proven vectors and reservoirs
- No vaccine
- No chemoprophylaxis
- Limited number of drugs with variable efficacy

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<th>Diseases Severity</th>
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<td><strong>No Tx</strong></td>
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| Small lesion, *L. major* or *L. mexicana* | IL antimonials
Liquid Nitrogen
Thermotherapy | Miltefosine | MA / SSG
Pentamidine
Amphotericin B | TT + MF
SbV + Allopurinol
SSG + Pentoxifylline |

Variable efficacy, high rate of AEs, lengthily schemes, low compliance

Topical & oral drug, safe, effective against all forms of CL, at a low-cost and be adapted for use in rural areas
CL Scarring, stigma and mental health problem
DNDi Cutaneous leishmaniasis strategy

To achieve short, safe, non-invasive, efficacious, affordable, and field-friendly treatments for CL or at least for lesions caused by *L. tropica* and *L. braziliensis*.
CpG ODN D35

- Patent owned by the US government and licensed to DNDi. D. Verthelyi, D. Klinman and K. Ishii are named as inventors on the patent covering D35 filed on April 1999.

- CpG D35 is a Class A (also know as class D) synthetic oligonucleotide, TLR9 agonist, designed to activate the innate immune system and enhance the effector mechanism to control *Leishmania* infection.

- It has been tested in a monkey CL model (with *L. major* and *L. amazonensis*) with encouraging results (reduction of pathogenicity, enhanced healing - even without an antiparasitic drug)

- Preclinical and CMC studies have been completed by DNDi with the support from GHIT and in collaboration with GeneDesign and Tokyo University

- First in human study (SAD in HV) is being conducted in UK and MAD in CL patients will start in mid 2022

- CpG D35 is planned to be administered for CL treatment in combination with an oral antiparasitic drug.

**Mode of Action**

- CpG D35 activates macrophages, inflammatory cytokines, allowing for anti-infective effects and NO production, cytotoxic T lymphocyte production.
- Activation leads to phagocytosis and death of the parasite, contributing to clinical healing.

*TLR9* activates *Monocytes* to produce **Inflammatory cytokines** (IFNγ, IL-12) and **Regulatory cytokines** (IL-10) which further stimulate the effector mechanism of the immune system.

**IP-10, IL-12, IFN-γ, IFN β, IFN-α** are key contributors in the effector mechanism against *Leishmania* infection.
CpG D35: A long Journey

- **1999** ODNs and their use to induce immune response, Patented by USG
- **2014 - 2015** DNDi Selection & Pre-clinical nomination
- **2016-2017** Preclinical efficacy
  - Characterization / Immunostimulatory effect of D35
  - Effect of D35 + Sb\(^V\) in healthy and Leishmania infected monkeys
- **2017-2020** Preclinical Development
  - Demonstrate the suitability of CpG D35 for progression to FIH.
- **2020-2023** Early clinical development
  - SAD / MAD studies
  - API formulation optimization
- **2023-2025** Phase II clinical study
  - Preliminary efficacy assessment
  - Safety in CL patients
- **2025-2027** Phase III clinical study
  - Effectiveness
  - Is it better than what’s already available?
- **2028** Registration

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www.dndi.org
CpG D35: A global collaboration of drug development expertise
CpG D35 in the time of COVID-19

COVID-19 has impacted in different ways the development of the project

• The lockdown and stay-at-home orders by the end of 2020 and beginning of 2021 caused a drop in the number of study participants, forcing the CROs to postpone the initiation of new studies.

• Many CROs were fully involved in conducting large studies on COVID-19 vaccines and not accepting new projects.

• Because the effects of CpG D35 in the immune system, an exclusion period of one month before and after receiving a COVID-19 vaccine has been imposed for all participants.

• The fear that CpG D35 interact with the host immune system is making potential participants being more hesitant to participate in a FIH study of an injectable product.
Lessons learned

• GHIT funds has created an especial environment with Japanese pharmaceutical companies and international organizations fostering global partnership committed to patients’ needs, creating medicines and vaccines against diseases for which there is a lack of R&D funding.

• Japanese pharma companies, research organizations and universities bring unique resources and capabilities including alternative drug discovery approaches, chemical classes not found abundantly in other libraries, technologies, insights and experiences gained through the whole process of product development.

• Oligonucleotides are not simple small molecules, so both the discovery and manufacturing require work with experts at the forefront of oligonucleotide. Having the opportunity to work with one of the creators of CpG D35 and with a pharma company with the expertise on GMP manufacturing oligos is exceptional and prized experience.

• Working in international environment always brings some challenges, often related to communication and culture, time zones differences and others but the politeness, diplomacy and Japan’s gastronomy compensates in abundance any of the challenges.
Thank You