R&D Demonstration Project

R&D demonstration projects were selected as per the Executive Board decision EB134(5) following review by the former Chair and Vice-Chair of the CEWG

1. Title of the project:
The Leishmaniasis Global R&D & Access Initiative- WHO Demonstration project

2. Proponent/s of the project:
Drugs for Neglected Diseases initiative

3. Project executive summary:
This project recommends the creation of the Leishmaniasis Global R&D & Access Initiative that will demonstrate that Leishmaniasis R&D projects can be optimized through guiding principles such as cross-regionals collaboration of existing networks, open-innovation and sharing knowledge, equitable access to new products, and sustainable funding secured through existing and new funding mechanisms.

Objective 1: to develop new safe and effective oral treatments as monotherapy and as early as possible as combination treatment (medical product) to prevent the risk of resistance development for the treatment of VL patients and a very safe, short-course one for asymptomatic carriers once their role in disease transmission has been better established:

Objective 2: to develop technology of diagnostic (xenodiagnoses coupled with a quantitative PCR) in order to evaluate the role in transmission of asymptomatic carriers and PKDL patients:

Objective 3: the development of treatment for PKDL (medical product) and completion of preclinical and clinical development of a selected immune response modifier which could be used in combination with chemotherapy for CL

Objective 4: the contribution to the development of a shared, open-access data base that will allow identifying determinants of treatment effectiveness that will be based on existing ones developed for malaria.

4. Innovative aspects of the project

Open-innovation and sharing knowledge
- The ‘Neglected Tropical Diseases Drug Discovery Booster’ consortium is circumventing early stage commercial barriers between the four pharmaceutical participants, allowing DNDi, for the first time to access to compounds generated over many decades of research to search millions of unique compounds simultaneously. On May 2015, four pharmaceutical firms, Eisai Co Ltd, Shionogi & Co Ltd, Takeda Pharmaceutical Ltd, and AstraZeneca plc have announced their participation. In February 2016, Celgene has become the fifth partner to join the NTD Discovery Booster Consortium. Any progress or successful new treatment resulting from the Drug Booster will be attributed to the collective effort of all partners, which have agreed that no IP barriers for NTD indications will be imposed
- De-risking and optimizing the investment at early stage: in order to control the risks of attrition at all stages of development and particularly at discovery-preclinical stage, DNDi has built a back-up pipeline for VL by developing a pipeline of molecules from different sources.
- Leishmaniasis clinical trial database by the IDDO (Infectious Diseases Data Observatory), previously known as World Wide Antipaludism Resistance Network (WWARN): the objective of this open access data base is to develop a global data-sharing platform for visceral leishmaniasis (VL) clinical trial data to improve intelligence on existing and new drug efficacy and treatment outcomes.

Equitable access to new products
Concerning the completion of preclinical and clinical development of a selected immune response modifier (CpGd35), a license with NIH (patent holder of CpG35) and CRADA (Cooperative Research And Development Agreement) with FDA were signed on December 2015. The terms and conditions of the license and agreement were negotiated following the DNDi license standards.

Innovative Regulatory pathways: In January 2015, the East African Community has opened up calls for joint reviews of registration dossier. The next step of this collaborative approach could be on clinical trial application and it is hoped that the VL LEAP study could benefit/use this new mechanism to support both a collaborative approach and also accelerate review time.

Sustainable funding secured through existing and new funding mechanisms

- Diversifying funding and leveraging new sources of funding: DNDi received 2.4 M from the WHO-TDR pilot pool funding. This allows leveraging additional and new donors funding (e.g. Brazil, South-Africa, India) beside usual bilateral grants. DNDi is also contributing in term of analysis and views to the study initiated by TDR for the set-up of a global pool funding. The Global Health Innovative Technology Fund (GHIT) is supporting the drug discovery booster, through a grant of EUR 572,000 for 3 years. The AFD (France) is supporting the VL initiative for an amount of EUR 2 M, DGIS (the Netherland) has also agreed to fund the Leishmaniasis initiative within a EUR 16 M grant covering also other diseases. Applications are pending decision with EDCTP2, focused on VL and with the German cooperation (BMBF) for several diseases including VL and CL.

5. The current status of the project

The project is in implementation phase and received a WHO-TDR award in August 2015 for one year. The project was already on going before August 2015, since it is based on an optimization and coordination of already existing initiatives.

6. Progress towards activities since the start of the project

Objective 1: to develop new safe and effective oral treatments as monotherapy and as early as possible as combination treatment (medical product):

Activity 1: 2 optimized lead have been nominated as preclinical candidate from 2 different series in Q4 2015 and Q1 2016. Continuous pipeline of leads is ensured.

Activity 2: Preclinical development activities have started for the first preclinical candidate in Q1 2016, the second one will start shortly.

Activity 3: Miltefosine PK study: The recruitment for the pharmacokinetics and safety of miltefosine allometric studies was completed in advance in November 2015 and data analysis is on-going.

Objective 2: to develop technology of diagnostic (xenodiagnoses coupled with a quantitative PCR) in order to evaluate the role in transmission of asymptomatic carriers and PKDL patients:

Activity 1: The preparation of the xenodiagnostic and quantitative PCR is on-going in Bangladesh. The building of the insectarium has been completed in SK hospital Mymensingh.

Activity 2: The infectivity study will focus on PKDL patients, not anymore on asymptomatics careers. The study will take place in Bangladesh, sites identification is on-going.

Objective 3: to develop treatment for PKDL (medical product):

Activity 1: The synopsis for the development of new regimen of treatments that demonstrate skin penetration for the current treatment of PKDL patient in Bangladesh and in India is completed and has been submitted to DNDi Scientific Advisory Committee that will take place in April 2016. The PKDL clinical trial synopsis for Sudan is final, pending review by the Investigator

Activity 2: CPG, an immune response modifier, API development has been delayed due to the different immune response between the Celgene produced API batch and the FDA produced batch. Further investigation is on-going to understand the difference and the API development work was put on hold.
A further application was made to the GHIT Fund for preclinical development activities up to FIH studies to include a preclinical efficacy study in the macaque CL model using CpG in combination with a partner drug (meglumine antimonate). This proposal was accepted and therefore we are including the macaque study in parallel of our already planned activities, to be started in July 2016.

**Objective 4:** the contribution to the development of a shared, open-access data base that will allow identifying determinants of treatment effectiveness that will be based on existing ones developed for malaria.

Afri-KA-treat (a consortium of 11 leading research institutions with extensive field experience from both Europe and East Africa) will establish the first leishmaniasis clinical trials data sharing platform under the umbrella of Infectious Disease Data Observatory (IDDO). The data-sharing platform will be co-managed by the DNDi Africa Regional Office in Nairobi and IDDO (University of Oxford). This collaboration has already been initiated: an EDCTP-TDR fellow from DNDi Africa Regional Office is currently in Oxford University for training on data management. The French Development Agency is partially financing the initial cost of the database creation.

**7. The first-round award received/expected from WHO based on the recommendation of the Ad Hoc Committee**

DNDi received 2.3 M EUR in August 2015

**8. Future developments and challenges**

**Objective 1:** to develop new safe and effective oral treatments as monotherapy and as early as possible as combination treatment (medical product) to prevent the risk of resistance development for the treatment of VL patients and a very safe, short-course one for asymptomatic carriers once their role in disease transmission has been better established:

*Activity 1:* Nomination of a third preclinical candidate before Q2 of 2017
*Activity 2:* The first preclinical candidate if successful will become a clinical candidate by Q2 2017 and the second if successful is expected to become a clinical candidate in Q4 2017.
*Activity 3:* The DDI fexinidazole-miltefosine study is expected to be finalized by Q1 2017. The Phase II/III clinical trial would then start in Q3 2017 in East-Africa.

**Objective 2:** to develop technology of diagnostic (xenodiagnoses coupled with a quantitative PCR) in order to evaluate the role in transmission of asymptomatic carriers and PKDL patients:

*Activity 1:* The renovation of the building for the establishment of the sand fly colony in Sudan will start in the second half of 2016 and the study will start in 2017.
*Activity 2:* The start of the infectivity study on PKDL patients is scheduled for the second half of 2016 in Bangladesh. Similar preparation activities will take place in Sudan later during the year for a study starting in 2017.

**Objective 3:** to develop treatment for PKDL (medical product) and CL:

*Activity 1:* In Q3-Q4 2016: development of the protocol, securing the local regulatory approvals for the clinical development of new regimen of treatments demonstrating skin penetration for the treatment of PKDL patients. The first patient first visit is scheduled for Q4 2016 in India and in Bangladesh. For Sudan, the synopsis is under finalization – expectation to start the study in Q4 2016/Q1 2017.
*Activity 2:* By end of 2017, all CMC and toxicologies studies will be completed and we will be ready to start First in Human studies of an immune response modifier for CL.

**Objective 4:** the contribution to the development of a shared, open-access data base that will allow identifying determinants of treatment effectiveness that will be based on existing ones developed for malaria.

Development of the basic data platform using available datasets from DNDi Africa and Asia offices; Q1-Q3 2016. Expansion of the data platform to include all available data, creation of a fully functional interactive internet presence with data visualization tools, and communications (start in Q4 2016).
The financial gap is currently estimated at 22 M EUR for 2016-2020.

9. Other sources of support
Existing other donors are:
DFID (UK), MSF and SDC (Switzerland) via core funding, KfW (Germany) and DGIS (the Netherlands) via portfolio funding, AFD (France) and GHIT (Japan) via projects funding, Bill and Melinda Gates foundation (US), Medicor, EU FP7, Kalacore (VL consortium DFID, UK)
Potential donors: EDCTP (EU), GHIT (Japan), BMBF (Germany)

10. Any additional comments
DNDi commit itself and partners in the CEWG R&D demonstration project process to evaluate and promote innovative mechanisms as well alternatives approaches to R&D that address pressing public health needs. That requires two important policy moves: 1) Increased financial and technical scientific resources, through new incentives and financing mechanisms; 2) reduced R&D costs, through open innovation mechanisms, public health-driven IP management, innovative regulatory strategies, and transparency of R&D costs. This project evaluate some of these incentives and principles s to support the progressive changes needed to re-orient the global biomedical R&D system so that it responds to patient needs.