DNDi
Drugs for Neglected Diseases *initiative*

Request for Proposal

Data Management, Biostatistics and IRT Services related to DNDI-LXE408-01-VL trial

Dated: August 2021

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Contents

1 PURPOSE

Novartis and the Drugs for Neglected Diseases initiative (DNDi) have signed a collaboration and licence agreement to jointly develop LXE408, as a potential new oral treatment for visceral leishmaniasis, one of the world's leading parasitic killers. If proven safe and efficacious, this therapy can be an attractive short-course oral option that can be used at any health care level in all foci of the disease. This will improve and simplify current case management and aims to reduce time between onset of symptoms and access to diagnosis and treatment, therefore reducing morbidity and mortality for the patient, and also reducing transmission and contributing to disease control and elimination.

DNDi plans to conduct a phase 2 clinical trial to assess the efficacy, safety and PK profile of LXE408. This trial will be conducted in India and will include 105 patients. It will be the first study in patients.

DNDi is the sponsor of the study and assumes the responsibility for the content of the Protocol.

2 DNDi OVERVIEW

2.1 Mission & objectives

Neglected tropical diseases continue to cause significant morbidity and mortality in the developing world. Yet, of the 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and tuberculosis, even though these diseases account for 11.4% of the global disease burden.

Founded in 2003 to address the needs of patients with the most neglected diseases, DNDi is a collaborative, patient's needs driven, not for profit drug R&D organization.

Acting in the public interest, DNDi bridges existing R&D gaps in essential drugs for these diseases by initiating and coordinating drug R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners.

DNDi's primary focus has been the development of drugs for the most neglected diseases, such as Human African Trypanosomiasis (HAT, or sleeping sickness), visceral leishmaniasis (kala-azar), and Chagas disease, while considering engagement in R&D projects for other neglected diseases to address unmet needs that others are unable or unwilling to address.

As defined within new Business Plan, the primary objective of DNDi is to deliver a total of 16 to 18 treatments by 2023 for leishmaniasis, sleeping sickness, Chagas disease, malaria, paediatric HIV, and specific helminth infections and to establish a strong R&D portfolio that addresses patient needs. Expanding upon R&D networks built on South-South and North-South collaborations, DNDi aims to bring medical innovation to neglected patients by developing field-adapted treatments.

In doing this, DNDi has two further objectives:

- Use and strengthen existing capacities in disease-endemic countries via project implementation
- Raise awareness about the need to develop new drugs for neglected diseases and advocate for increased public responsibility.

For more information, please visit DNDi website: http://www.dndi.org/

2.2 Project background

Visceral Leishmaniasis (VL), also known as kala-azar in the Indian sub-continent, is caused by the protozoan parasites *Leishmania donovani* and *Leishmania infantum*, with a distribution in Asia, East Africa, Latin America and the Mediterranean region. The natural history of VL is of a complex nature comprising various elements fueling transmission: poverty, HIV-VL co-infection, PKDL, climatic changes, zoonotic reservoirs (mostly known but in some areas only suspect) and –to be proven- asymptomatic carriers. In Asia and Africa VL is anthroponotic meanwhile in America it is zoonotic with the dog as the main reservoir.

There are a few treatment options available to VL patients and unfortunately, all of these drugs suffer from significant drawbacks of either parenteral route of administration, length of treatment (21 to 28 days), toxicity or cost, which limit their use in disease-endemic areas.

The development of novel oral therapies with high efficacy and good safety profiles alone and in combination are essential. New chemical entities (NCE) are in clinical development phase.

This study aims to assess the efficacy, safety and PK profile of LXE408, a NCE, in primary VL patients in India. If proven safe and efficacious, this therapy can be an alternative. It would be an attractive short-course oral option that can be used at any health care level in all foci of the disease.

The present request for proposal concerns Data Management, IRT and Biostatistics Services.

2.3 Phase 2 Clinical trial: Key data

- Indication: Visceral Leishmaniasis
- Study design: This is a phase II, multicentre, randomized, two-arm blinded study with an open label calibrator arm in adults and adolescents (≥12 years) with confirmed primary VL.
- Objective of the study: The overall objective of the study is to assess the efficacy, safety and pharmacokinetic parameters of LXE408 and AmBisome, the Standard of Care
- No. of participating countries: 1 country (India)
- Participating sites: 2 sites
- Number of patients planned: 105:
    - 95 adult patients enrolled in a 2:2:1 ratio to one of the 3 following treatment arms
        - Arm 1 (up to 38 patients): LXE408 q24h for 7 days followed by 7 days of placebo q24h
        - Arm 2 (up to 38 patients): LXE408 q24hr for 14 days
        - Arm 3 (19 patients): Standard of Care AmBisome, one single dose (SDA)
    - 10 adolescent patients enrolled in a 1:1 ratio to one of the 2 following treatment arms
        - Arm 1 (5 patients): LXE408 q24h for 7 days followed by 7 days of placebo q24h
        - Arm 2 (5 patients): LXE408 q24hr for 14 days

- Recruitment Plan:
    - Number of subjects to be enrolled: 105 patients
    - Duration of Recruitment: approximately 12/13 months (about 8 patients/month)
    - Duration of Follow up/patient: 6 months after 1st dose

- Study design:

The study will start with enrolment of adult patients: approximately 95 adults will be enrolled in a 2:2:1 ratio to one of three treatment arms.
One interim analysis (IA) will be performed. After this IA, recruitment in LXE408 arm may be expanded to a sub-group of approximately 10 adolescent VL patients, upon recommendation from an independent Data Monitoring Committee (IDMC).

3 RFP INSTRUCTIONS

3.1 General Information

a) DNDi invites you, as a service provider, to submit a proposal to support DNDi activities described in the section Scope of Work. The issuance of this current Request for Proposal (RFP) in no way commits DNDi to make an award. DNDi is under no obligation to justify the reasons of its service provider's choice following the competitive bidding. DNDi could choose not to justify its business decision to the participants of the RFP.

b) This entire RFP and all the related discussions, meetings, information exchanges and subsequent negotiations that may occur are subject to the confidentiality terms and conditions of the Intent to Participate Letter attached as Appendix 1.

c) All bidders are required to complete, and send return the Intent to Participate letter.

d) The issuance of this current RFP in no way commits DNDi to make an award. DNDI is under no obligation to justify the reasons of its service provider's choice following the competitive bidding. DNDi could choose not to justify its business decision to the participants of the RFP.

e) DNDi reserves the right to:
- Reject any proposal without any obligation or liability to the potential service provider.
- Withdraw this RFP at any time before or after the submission of bids without any advance notice, explanation, or reasons.
- Modify the evaluation procedure described in this RFP
- Accept other proposal than the lowest one
- Award a contract on the basis of initial proposals received without discussions for best and final offers
- Award all services to only one supplier or allocate them to different suppliers according to what DNDi will consider necessary

f) Late submission proposals are subject to rejection

g) DNDi reserves the right to request additional data, information, discussions, or presentations to support their proposal. All bidders must be available to discuss about details of their proposal during the RFP process

h) A proposed time plan set out below indicates the process DNDi intends to follow. If there are changes to these timelines, DNDi will notify you in writing.

3.2 Timelines

Process Steps	Responsible Party	Timelines
RFP Launch	DNDi	August 16th 2021
Send back the LoI signed	Service Provider	August 23rd 2021
Send the protocol to CROs	DNDi	August 23rd 2021
Questions sent to DNDi	Service Provider	August 31st
DNDi responses to Q&A	DNDi	September 7th
Reception of proposals	DNDi	September 22nd
Notification to Pre-selected Bidders	DNDi	October 8th
Bid defense meetings	DNDi & Service provider	October 15th
Project award	DNDi	November 1st 2021
Project start	Service Provider	Upon contract signature

3.3 RFP processes and contacts information

3.3.1 Confirmation of Intent

Please transmit your intent to participate by using and signing the document attached in Appendix 1.
Each bidder is required to provide DNDi with a written confirmation of intent or decline to participate by the date as indicated in the section 2.2.
Confirmations of intent should be sent by email to Christophine Marty-Moreau (contacts details below).
Please note the "Intent to participate letter" is a standard document which DNDi cannot afford negotiating due to project priorities, time and resources dedication. This template is based on several years of experiences working with services providers and contains widely acceptable terms.

3.3.2 Questions

All bidders may request further clarifications in regards of this current RFP, by addressing its questions in writing to the dedicated key contacts identified below. These questions should be submitted to DNDi at the date mentioned in the below table.

In order to keep a fair bidding process, questions on the substance will only be answered in a document shared with all the bidders on the date indicated in section 3.2. To submit your questions, please use the form attached as Appendix 2.

Questions types	Contact Person/Title	Contact Information
Contractual & Business aspects	Christophine Marty-Moreau Senior Procurement Manager	15 Chemin Camille Vidart, 1202 Geneva, Switzerland Phone : +41 22 906 92 61 Email : cmarty@dndi.org
Clinical Trial Management	Gwenaelle Carn Senior Clinical Project Manager	15 Chemin Camille-Vidart, 1202 Geneva, Switzerland Phone : +41 22 555 19 95 Email : gcarn@dndi.org

3.4 Format and content of the proposal

Responses to this RFP must be in English and should contain the following information:

- ✓ Administrative information e.g.
  - o Management team, history, key contacts and specific business approach with NGOs
  - o Key figures (business turn over and headcounts for the past 3 years, financial stability, company locations)
  - o Customer's reference in related area

- ✓ Technical proposal e.g.
  - o Detailed proposal detailing the services and explaining how your company approach will enable to meet project timelines and ensure quality results.
  - o Detailed presentation of the team and organization proposed to answer the needs described above
  - o Samples of CVs from key team members
  - o Any other relevant information (recommended IT tools and platforms, etc.)

- ✓ Financial proposal
  - o DNDi Budget template to be completed (attached in Appendix 3) for all 3 activities plus a project costs summary
  - o If your company has to sub-contract some activities, please indicate those clearly in the budget without forgetting the names of your providers.

- ✓ Any other relevant information enabling DNDi to assess the opportunity of contracting with your company

3.5 Conflict of Interest

The Company shall disclose any actual or potential conflicts of interest in the Intent to Participate letter.

4 SCOPE OF WORK

4.1 Data Management

4.1.1 General Information

DNDi will provide the CDISC CRF created with IDDO (Infectious Diseases Data Observatory). This template will facilitate the creation of the database.

DNDi would like an easy collection and a rapid transmission of study data in remote centres, where internet access might be limited.

- ✓ Data management systems must be compliant with 21 CFR Part 11
- ✓ Dataset to be compliant with CDISC (SDTM, ADaM) format (template provided by DNDi)
- ✓ English eCRF, EDC system (i.e. interface)
- ✓ English data handling (e.g. data review, queries)
- ✓ English support and documentation
- ✓ Offline capability a plus, at least tolerance to low bandwidth and high latency (lightweight interface)
- ✓ Targeted SDV requirement (page or item level)
- ✓ Data (population set, reason for non-inclusion, demographics, AEs, queries sent with answers to queries…) and metrics (database status, enrolment status, sites metrics, etc…) available to Sponsor through online system

- ✓ For screen failures: informed consent, demographics, adverse events, and reason for screen failure will be captured

4.1.2 Main Data Management Activities

A summary of the main activities is detailed below (list not exhaustive):

- ✓ eCRF development, implementation, and maintenance
- ✓ Data Management Plan development and maintenance
- ✓ eCRF completion guidelines development and maintenance
- ✓ Annotated CRF development and maintenance
- ✓ Data Validation Plan development and maintenance
- ✓ Database design and set-up (eCRF page, dynamism, branching, programmed edit checks, reports, etc..), deployment, maintenance, and archive
- ✓ User acceptance testing
- ✓ Site, CRA and DNDi training on eCRF use, completion, and data cleaning process
- ✓ eCRF help desk support with a dedicated chat, email, phone number and/or IM option
- ✓ Data review and validation
- ✓ Data cleaning
- ✓ Monitoring and reporting of data entry and CRF tracking
- ✓ Medical review
- ✓ Coding set-up (latest versions of MedDRA and WHO Drug + updates)
- ✓ Medical coding
- ✓ Serious Adverse Event reconciliation
- ✓ Lab transfer specifications and management of lab data importation (e.g. central lab, PK and additional lab data (qPCR, LAMP, transcriptomics), randomization list)
- ✓ Reconciliation and cleaning of all lab data on an ongoing basis as defined in the data management plan (DMP)
- ✓ Data export to third parties
- ✓ Provide raw data extracts upon request
- ✓ Management of blinded and unblinded data including measures to protect the blind
- ✓ Preparation and review of data prior to the database locks, IDMC meetings and other study deliverables (such as annual safety reporting)
- ✓ eCRF progress reports edition
- ✓ Clinical data listings and patient profiles generation (including queries tracking for each patient)
- ✓ Protocol deviations tracking and reporting
- ✓ Pre lock Data review meeting preparation, organisation and documentation
- ✓ Database lock
- ✓ Data Management Report
- ✓ Deliver CDISC ready submission package to sponsor, including but not limited to SDTM datasets (including Define XML and SDTM reviewers guide), datasets, annotated CRF, CRF
- ✓ On going Data management files for TMF maintenance and upload into the sponsor e-TMF
- ✓ Transfer of all completed eCRFs to the purpose of full CSR preparation

Those points are to be detailed in the proposal:

- ✓ Access a demo instance of the EDC system proposed
- ✓ Patient identifier number assignment and registration process
- ✓ eCRF feature regarding visit, page and visit dynamisms and cross pages programmed queries
- ✓ Specifications and development review and approval
- ✓ How to address lightweight interface or low-income settings compliance (latency, low bandwidth)
- ✓ Data entry and how DNDi, sites and monitors will have access to study data

- ✓ eCRF Help desk support (e.g. method of communication, time coverage, language)
- ✓ eCRF Data validation (e.g.: automated vs manual, by allocating time continuously or when you have the full patient profile) and expected turn-around time for query resolution
- ✓ Protocol deviations identification and reporting process
- ✓ Database lock activities (e.g. including data review meeting with DNDi and timelines)
- ✓ Examples of Progress report, clinical data listings, Patient Profiles and data/metrics available online
- ✓ Budget detail

4.1.3 Other Data Management Activities

To support the study management and follow-up

- ✓ Edit and send (study team + investigator) electronic visit calendar for each patient included.
- ✓ Send reminder for FU visits (study team + investigator)
- ✓ Send reminder for missing visits (study team + investigator)
- ✓ Online access to study data (clean and unclean data – based on 'Optional extra') allowing remote monitoring

Reports:

- ✓ Query reports to CRAs and investigators
- ✓ If not available online, listings of data as required (population set, reason for non-inclusion, demographics, AEs…) and reports on metrics (database status, enrolment status, sites metrics, etc…). Reports should be ready for implementation since first patient in order to follow the study progress. Ensure flexibility for unscheduled demands.
- ✓ Data Review Plan including the full list of reports that will be generated to support management and data cleaning of the trial

4.1.4 DNDi-LXE408-01-VL Assumptions

Sites	2
Countries	India
Number of patients	105 patients
Recruitment rate	About 8 patients/month; 12/13 months to recruit the patients
Unique eCRF pages	About 50 pages/patient (see schedule of events)
Nb of AEs	3 AEs/patient => About 315 AEs
Nb of SAEs	10
Nb of queries	Automatic queries: about 10000 Manual queries: about 5000
Medical Coding	500 MedDRA codes (medical history and adverse event) 500 WHODRUG codes (prior and concomitant medications)
SAE reconciliation	Quarterly (6)
IDMC	1
Database Lock	1 An additional interim data base lock (DBL) may be scheduled at completion of the adult treatment arms if recruitment of adolescents takes significantly longer.

The Clinical Trial Protocol with the confidential information will be shared after the receipt of the LoI signed.

4.2 Interactive Response Technology (IRT)

Those IRT capabilities are to be considered:

- ✓ "Patient screening" and "enrolment and randomization" as separated transaction
- ✓ Patient screening: site should be able to input information about the patient, year of birth or age
- ✓ Enrolment and randomization:
    - confirmation that the patient has passed screening procedures
    - IRT should also not allow adolescents until the IA is complete
    - To create 2 randomization schedules: randomization to one of the 3 arms (2:2:1) for adults or one of the 2 LXE408 arms (1:1) for adolescent patients, and based on the input year of birth/ age from Patient Screening
    - Treatment assignment. For LXE408 arms, as the treatments will be blinded, the dispensation will be by bottle #.
    - IRT to notify the first 20 adult patients that need intensive PK (IRT to inform if patient is intense PK or regular PK).
  - ✓ Possibility to remove or add 1 arm after IA
  - ✓ Drug management:
    - acknowledgement of the drug and released once it arrives on the site,
    - activation of the site to dispense drugs when the drug is on site,
    - inventory management to ensure site has sufficient drugs to enrol new patients,
    - Automatic resupply
    - Drug replacement: for lost or damaged drug. System can replace with new packs
  - ✓ Link to the data management system for vial # reconciliation

4.3 Biostatistics and Statistical programming

4.3.1 General Information

- ✓ CDISC (ADaM)
- ✓ The study statistician should be blinded
- ✓ Another unblinded statistician should be part of the study in order to provide unblinded safety, efficacy and PK interim data to the independent data monitoring committee

4.3.2 Biostatistics and Statistical programming - Main Activities

- ✓ Statistical analysis plan (SAP) development, maintenance and finalization
- ✓ Data definition and Analysis dataset programming
- ✓ Programming and validation of tables, listings and figures
- ✓ Blinded report for IDMC
- ✓ Statistical analyses
- ✓ Production of statistical tables, listings and figures for IDMC and final analysis (after having dry runs)
- ✓ Statistical report
- ✓ Statistical collaboration and input on the CSR including pdf integration
- ✓ Deliver ADaM datasets (including Define XML and ADaM reviewers guide)

4.4 Project Management

- ✓ Kick-off meeting
- ✓ Participation to investigator and monitor meetings

- ✓ Review of study protocol, amendments, and clinical study report
- ✓ Organize (agenda) and report (minutes) :
  - Meeting with DNDi: Weekly during the set up then monthly
  - Data review meeting (quarterly)
  - Protocol deviation review meeting (quarterly)
  - Unscheduled meeting or communication with the sponsor
- ✓ Risk assessment and mitigation and metrics analysis

5 CRITERIA FOR SELECTING SERVICE PROVIDERS

The decision to award any contract resulting from this RFP process will be based on Service Providers' responses and any subsequent negotiations or discussions.
The decision-making process will consider the ability of each service provider to fulfil DNDi's requirements as outlined within this RFP and the cost of the offer.

Proposals will be assessed against the main following criteria but not limited to:
Technical criteria

- Project approach, methodology and planning
- Experiences/skill level of company representatives assigned to this project
- Quality and applicability of proposal presentation
- Customer references / Experience in related area and country

Capacity to deliver

- Capacity to deliver the services
- Ability to meet timelines
- Project Management capabilities
- Track record and references for similar projects and in similar countries/context
- Risk Management approach

Financial criteria

- Realistic costing of the project and strategy to minimize expenses
- Costs and deliverables per set of activity
- Costing strategy/proposal non-for-profit organizations

6 STUDY TIMELINES

Activities	Estimated timelines
Final protocol	14 July 2021 (completed)
CRF template for regulatory submission	21 July 2021(completed)
Regulatory Submission	August 2021
Regulatory Approvals	February 2022
Final IRT	February 2022
Final eCRF	February 2022
Final SAP approved by DNDi	February 2022
Database set-up, tested and ready to go live	February 2022
Final DM Document (e.g. DMP, DVP) approved by DNDi	February 2022
First Subject First Visit	March 2022
First Subject First Dose	March 2022
Last Subject Last Dose	March 2023
Last Subject Last Visit	September 2023
Database Lock	November 2023
Top Line Report	December 2023
CSR	February 2024

7 APPENDICES

Appendix 1: Intent to Participate Letter (LoI) template

Appendix 2: Q&A form

Appendix 3: Budget grid template

Appendix 4 : Clinical Trial Protocol will be shared after the receipt of the LoI signed