DNDi
Drugs for Neglected Diseases *initiative*

Request For Proposal

A PHASE 1, BLINDED, RANDOMIZED, SINGLE CENTRE, PARALLEL-GROUP, MULTIPLE-DOSE, DOSE-ESCALATION, PLACEBO-CONTROLLED STUDY OF THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF DNDI-6148 AFTER ORAL DOSING IN HEALTHY MALE AND FEMALE SUBJECTS

Dated: March 1st 2022

Table of Contents

1 PURPOSE

The evaluation is requested by DNDi (Drugs for Neglected Diseases *initiative*).

DNDi would like to conduct in India a Clinical phase 1 study to assess safety, tolerability and pharmacokinetics after multiple dosing (MAD) of an investigational product.

One compound is to be tested.

2 RFP INSTRUCTIONS

2.1 General information

a. DNDi invites you as a Service Provider to submit a proposal in regards of this RFP for conducting this phase 1 study.

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 attached as Annex 1.

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

d. The issuance of this current Request For Proposal 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 to allocate them to different suppliers according to what DNDi will consider necessary and
- Confirm the award after the results of the Qualification GCP Audit.

f. DNDi and the selected service provider will be required to adhere to DNDi's donor's requirements including:
- Frequency and format of financial and technical reporting
- Access to financial records and audits
- DNDi to own the resultant IP
- Confidentiality obligations surviving termination/expiry

g. Late submission proposals are subject to rejection.

h. 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.

i. All offers should be submitted in an electronic format.

j. 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.

2.2 Timelines

Process steps	Responsible party	Timelines
Launch RFP (including questionnaire)	DNDi	1 March 2022
Send back the Intent to Participate letter signed and the technical questionnaire fully completed	Service Provider	8 March 2022
Send the study synopsis to CROs	DNDi	15 March 2022
Questions sent to DNDi	Service Provider	22 March 2022
DNDi responses to Q&A	DNDi	25 March 2022
Reception of proposals	DNDi	8 April 2022
Notification to Preselected bidders	DNDi	15 April 2022
Bid Defence Meetings	DNDi / Service Provider	22 April 2022
Due Diligence	DNDi	22-29 April 2022
Project award	DNDi	29 April 2022
Qualification GCP Audit	DNDi	May-June 2022
Start-up Agreement	DNDi / Service Provider	29 June 2022
Final Protocol signed	DNDi / Service Provider	24 August 2022
Full Clinical Trial Agreement Execution	DNDi / Service Provider	24 August 2022
CTA protocol submission package	Service Provider	31 August 2022

2.3 RFP processes and contact information

2.3.1 Instructions

All bidders may request further clarifications in regards of this current RFP, by addressing questions in writing to the dedicated key contacts identified below. These questions should be submitted to DNDi at the date mentioned in the section of 2 of the RFP.

In order to keep a fair bidding process, questions on the drugs to be assessed will only be answered anonymously in a document shared with all the bidders on the date indicated in section 0 of the RFP

To submit your questions, please use the form attached as Annex 3.

2.3.2 Confirmation of Intent & technical questionnaire

Please transmit your intent to participate by using and signing the document attached in Annex 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, with the technical questionnaire fully completed.

Please, note that 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 experience working with suppliers and contains widely acceptable terms in RFPs.

Confirmations of intent should be sent by email to Christophine Marty-Moreau (contacts details below).

Questions types	Contact person	Title	Contact information
Contractual & Technical aspects	Christophine MARTY MOREAU	Senior Procurement Manager	15 Chemin Camille-Vidart, 1202 Geneva, Switzerland Phone: +41 22 906 92 61 Email: cmarty@dndi.org

2.4 Format and content of the proposal

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

- **A cover letter including:**
  - Name and address of the service provider
  - Name, title, phone number and email address of the person authorized to commit contractually the service provider
  - Name, title, phone number and email address of the person to be contacted in regards of the content of the proposal, if different from above
  - Signature of this letter done by a duly authorized representative of the company
  - Acceptance of the consultation principles as detailed in section 2.1

- **A technical proposal**
  - Detailed proposal explaining how your company approach will enable DNDi team to meet project timelines and ensure quality results.

- **A financial proposal**
  - DNDi Budget template to be completed and attached as Annex 4.
  - Service provider's budget template can be provided in addition to the DNDi budget template. It cannot replace the proper filling of the DNDi budget template.
  - All amounts shall be stated to be inclusive of GST and all other applicable taxes and any other indirect costs

- **Administrative information**
  - Business Company information: directors and officers, creation date, corporate headquarters, locations, business turnover of the past 3 years (global and in the field of service provided), headcounts (global and in the field of service provided), general services provided, customer's reference, pricing strategy for NGOs…
  - Any other relevant information enabling DNDi to assess the opportunity of contracting with your company.

2.5 Conflict of Interest

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

3 DNDi OVERVIEW: Mission & objectives

Neglected tropical diseases continue to cause significant morbidity and mortality in the developing to patients in the developing world in addition to a significant socioeconomic impact.

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

DND*i*'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.

To date DNDi has delivered 8 novel treatment to patients suffering from malaria, Leishmaniasis, HAT, peadiatric HIV, and Chagas disease, with the ambition to deliver in total 16 to 18 new treatments by 2023 and to establish a strong R&D portfolio that addresses patient needs. Expanding upon R&D

networks built on collaborations with disease endemic countries, DNDi brings medical innovation to neglected patients by developing field-adapted treatments.
In doing this, DNDi has two additional objectives:

- Use and strengthen existing capabilities 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/

4 SCOPE OF WORK

Drugs for Neglected Diseases initiative (DNDi) is currently developing a New Chemical Entity in the indication of Visceral Leishmaniasis (VL), the benzoxaborole DNDI-6148.

Visceral Leishmaniasis, also known as kala-azar, 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 fuelling 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 these drugs suffer from significant drawbacks of either parenteral route of administration, length of treatment (21 to 28 days), variable efficacy, 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.

The present request for proposal concerns a multiple ascending dose study to assess safety, tolerability and pharmacokinetic of DNDI-6148 after oral administration of doses to healthy volunteers during 10 days.

Pre-clinical package to support Phase I is sufficiently complete to support healthy volunteers' studies. The Single Ascending Dose study showed a good safety profile in male healthy volunteers, as well as good exposure in volunteers. The data of the MAD will be critical in the decision to move forward into Phase II in patients. First Subject First Visits (screening) for this MAD study are planned for early January 2023.

DNDi will provide as documentation the IMPD, Investigator Brochure, Clinical Study Synopsis, and packaged IMP once the service provider awarded.

4.1 Phase I MAD Clinical trial: Key data

Indication: Visceral Leishmaniasis

Study design: Multiple Ascending Dose study in Healthy volunteers

Objective of the study: The overall objective of the study is to assess the safety, tolerability and pharmacokinetic parameters of DNDI-6148

No. of participating countries: 1 country, India

Participating clinical sites: 1 site

4.2 Short presentation of the compound

The NCE to be tested will be DNDI-6148, arginine monohydrate, a 6-substituted benzoxaborole compound.

4.3 General Information on the Phase I MAD study

- Healthy volunteers between 18 and 50 years, inclusive.
- Male or Female of non-child-bearing potential
- It is expected that no special population will be required.
- As the synopsis is in a draft form, some aspects of the study design will be confirmed at a later date. In that case, please provide information in the proposal on the alternative options specified below.

❖ **Screening**

Screening to include standard Phase I parameters (e.g. physical examination, neurological examination, vital signs, body temperature, medical and surgical history, alcohol/drugs of abuse screening, ECG, haematology, haemostasis, hormonology, chemistry, urinalysis, etc.), serology for: HIV 1/2, HBsAg, and HCV antibody (see detailed and complete list in the draft synopsis/schedule of events).
The day of admission at the Phase I Unit, the same procedures will be repeated as well as a Reverse Transcriptase Polymerase-Chain-Reaction (RT-PCR) test SARS-CoV-2 to minimize the risk of a healthy volunteer to contaminate any other volunteer and/or facility staff, as well as avoiding the risk for a volunteer already in the incubation phase without symptoms to get exposed to the IMP.

❖ **Main Study**

Similar procedures will be repeated during the course of the study.
Assessment of TNF alpha and CRP will be performed prior and post-dosing during specific days during the course of the study.

This study is a Randomized, double-blind, placebo-controlled, multiple oral administration, ascending dose.

The IMP (DNDI-6148 and the placebo) will be available as a powder for oral administration and a suspension will be prepared extemporaneously by the pharmacist prior to administration to the volunteers. The powder will be suspended in ORA-Sweet® vehicle, a maximum of 24 hours prior to dosing.

After randomisation, each cohort will start with 2 sentinel subjects (one under active formulation, one under placebo). Once the sentinel subjects will have completed the study (with no safety concern and in agreement with the sponsor), the remaining subjects will be included in the dosing group.

The subjects will arrive at the clinical unit in the morning on Day -1 for baseline assessments and will be hospitalized after admission up to D14 once the follow up visit will be done.

	DNDi-6148
Number of cohorts planned	3 cohorts (+ 1 extra as optional)
Number of subjects/cohorts	10 subjects per cohort (7 active/3 placebo)
Number of subjects planned	30 subjects (+ 10 potential additional volunteers for the optional cohort)
Duration of recruitment	6 months (FSFV: January 2023 / LSLV: July 2023)
Duration of dosing	10 days
Duration of Follow up	4 days after last dose

Standard safety monitoring procedures inclusive (e.g. AE, vital signs, ECG, haematology, chemistry, urinalysis etc.)
Specific assessments will be provided with the draft synopsis/schedule of events:

- Central ECG reading by third party based in Europe
- Assessment of CRP and TNF alpha (pre-dose and 6h post dose) at specific days during the course of the study

❖ PK sampling

- Plasma and urine samples to be collected and shipped possibly to a third party for bioanalysis.
- For each subject at each dose level, blood will be collected at the time points defined in the synopsis.
- Urine will be collected during the intervals defined in the synopsis.

❖ Other Information

- IMP storage conditions: between 15°C and 25°C - Do not freeze.
- IMP Bottles of pre-weighted powder of DNDI-6148 arginine monohydrate (corresponding to 600 mg free acid equivalent) and corresponding placebo will be provided to the pharmacy's site by DNDi. The administration will be performed around 8:00 a.m. on each dosing day in sitting position and in fasting conditions. 250ml of tap water will be ingested after dosing. The same procedure as for the active drug will be followed for extemporaneous preparation of placebo.
- Safety ECGs will be generated and read at the clinical site and then transmitted to read by cohort by a third-party service provider based in Europe and already identified by the sponsor for central reading. Interim cardiac safety reports will be provided by the third-party. Data analysed will be transferred in the clinical database at the end of the study to be included in the CSR.

- Holter devices will be provided by the sponsor. ECG devices from the service provider can be used, provided they allow electronic transfer of recordings to the third-party.
- Randomization list to be provided by service provider as well as statistical input on the synopsis/protocol.

❖ **Statistical Methods**

- Safety:

Safety Population will be represented by all subjects who received at least one dose of IMP. All safety parameters (ECG, vital signs, AEs, etc.) will be summarized by dose level and time point.

- PK:

PK Concentration Population will be represented by all subjects who received at least one dose of IMP and for whom a pharmacokinetic sample has been analyzed. PK Parameter Population will be represented by all subjects in the PK Concentration Population for whom pharmacokinetic parameters can be derived. All plasma concentrations will be summarized by dose level. The derived PK parameters will be listed by subject and summarized by treatment or by dose level.
Plasma concentrations and PK parameters of the NCE and corresponding metabolites will be listed and summarized, by treatment, using descriptive statistics. Individual and mean plasma concentration–time profiles will be presented graphically.

4.4 List of activities to be performed

- Review of draft synopsis – technical input
- Protocol writing
- Volunteer Information Sheet and Consent Form Writing
- Insurance coverage to be provided
- Public disclosure of the trial via Clinical Trials Registry – India (ctri.nic.in)
- Regulatory and Ethics Committee submissions – Information of the Sponsor in case of regulatory updates during the conduct of the study.
- CRF design (eCRF)
- Storage and management of IMP, including preparation of IMP, accountability and return to sponsor or designee (please also include an option to destroy IMP onsite or through 3rd party)
- Pharmacy manual writing
- Technical input on labelling as per local requirements (validation of labels proposed by Sponsor ahead of labelling procedure)
- Randomization list: to be generated by Service Provider
- Clinical conduct: subject recruitment, screening, dosing, and all clinical procedures detailed in section 4.1. and draft synopsis
- Biometrics (database design, data entry, data management, data cleaning, and statistical analysis)
- Project Management of activities conducted by the Service Provider, including required plans for the activities where applicable (e.g. DMP, Monitoring Plan, SAP etc.), organization of Kick-off meeting and weekly communication with the Sponsor representative, including communication plan with clear escalation path for major/critical finding

- Clinical Trial Monitoring, including supervision of monitoring activities by the service provider Project Manager
- Labelling and shipping of PK samples (frozen) to a bioanalysis service provider (based in India). Service Provider will prepare the plasma and urine samples and ship them to a third-party contracted by the Service Provider for the bioanalysis.
- PK report: Data to be transferred back to the Service Provider and sent to a third party in Europe already identified by the sponsor for PK data interpretation (for preparation of interim plasma PK report that will be used for the dose escalation decision).
- Storage of PK back-up samples and plasma/urine left-over (frozen) up to the end of the study (up to a maximum of 3 months after LSLV) – Capacity to destroy the samples after written approval of the Sponsor
- Pharmacovigilance, DSUR: Managed by DNDi – forms and safety management plan to be provided by DNDi
- Sponsor eTMF set-up and maintenance on a regular basis (access to the system and training will be provided by the sponsor), regular completeness checks in view of possible inspection
- Investigator Site Documentation
- Legal representation of the sponsor in the country as required
- Compliance with applicable data protection legislation

4.5 Expected reporting

- Study Status Reports (weekly): start-up progress, recruitment, data cleaning
- Meetings: weekly telephone meetings with the sponsor, kick-off meeting, minutes
- Interim Safety Reports (before each Safety Review Committee meeting)
- Interim PK Reports
- Safety Review Committee organization (dose escalation meetings, ad hoc in case of safety issue)
- Clinical Study Report writing (3 drafts, one final version)
- Data transfer (database and other documents transferred to Sponsor on CD-Rom or equivalent electronic support at the end of the Study).

5 CRITERIA FOR SELECTING SERVICE PROVIDERS

The decision to award any contract as a result of this RFP process will be based on Service Providers' responses, subsequent negotiations or discussions and a successful audit. 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:

5.1 Technical criteria

- ✓ Facilities and license to perform MAD studies in India
- ✓ Facilities and adequate personal to prepare IMP
- ✓ Potential female healthy volunteers in service provider's database that could be included in the study
- ✓ Records of Audits/Inspections of the facilities/processes

5.2 Capacity to deliver

- ✓ Reasonable timelines including at least but not only the ones related to recruitment, and regulatory and ethics committee submissions. Where applicable, please specify projected timelines in the proposal, including 'best case' and 'worst case'.
- ✓ Capacity to respect timelines for dose-escalation (screening of volunteers, shipping of samples, availability of interim PK and safety reports, etc…)
- ✓ Access to subject population
- ✓ Project management capabilities and experience
- ✓ Past experience with similar activities
- ✓ Experience with DNDi
- ✓ Profile of staff involved (CVs)

5.3 Financial criteria

- ✓ Realistic costing of the proposal with NGO rates when possible

6 PROPOSAL REQUIREMENTS, DELIVERABLES & TIMELINES

6.1 Proposal requirements

Following the issuance of the RFP, all interested bidders are invited to submit a proposal that describes:

- ✓ General information of the company as described in section 2.4
- ✓ Technical and financial proposal as described in section 2.4. Budget with full details of your offer including fixed costs and Pass-Through Costs. We recommend the use of DNDi template inserted as Annex 4.
- ✓ Whole project timelines including Regulatory and Ethics submission and approval (taking into account holiday period as applicable)
- ✓ Project team involved
- ✓ List of tasks and responsibilities

In addition, please provide us with complementary information on:

- ✓ Standard QA package recommended by the Service Provider (e.g., audits, QC procedures etc.)
- ✓ Proposals for monitoring scope and schedule
- ✓ Options to front-load activities in order to gain time (e.g., pre-screening)
- ✓ Service Provider facilities for re-labelling (following shelf-life extension) if required
- ✓ TMF Documentation maintenance, QC, and transfer to sponsor

6.2 Deliverables

- ✓ Comments on draft synopsis
- ✓ Protocol
- ✓ ICF
- ✓ Pharmacy Manual
- ✓ eCRF/CRF, Data Management Plan, database specifications and edit-checks, Cdisc format
- ✓ Regulatory and Ethics Committee Submission/Approval
- ✓ Safety Interim Reports
- ✓ PK laboratory
- ✓ Periodic study status reports detailed in section 4.2

- ✓ Monitoring visit reports
- ✓ Data management report
- ✓ Complete package of TMF documentation, for all activities managed by the Service Provider
- ✓ Final Clinical Study Report
- ✓ Database CDISC/SDTM/ADaM format
- ✓ Any other document/activity required to ensure the conduct of the study to the highest level of quality (please specify)

6.3 Timelines

- Beginning of services planned in July 2022
- Completion of clinical activities is planned by end of 2023 (with final CSR)
- Proposed timelines for the whole project are required for internal planning (include both 'best case' and 'worst case' options).

7 ANNEXES

Annex 1: Intent to Participate letter

Annex 2: Technical questionnaire

Annex 3: Q&A Form

Annex 4: Budget template