Request For Proposal

PHASE I STUDY
OF SAFETY, TOLERABILITY, AND
PHARMACOKINETICS AFTER MULTIPLE ORAL
ASCENDING DOSES OF DNDI-0690

Dated: May 2020
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1 PURPOSE

The evaluation is requested by DNDi (Drugs for Neglected Diseases initiative). DNDi would like to conduct in the UK 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 both phase 1 studies.

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

<table>
<thead>
<tr>
<th>Process steps</th>
<th>Responsible party</th>
<th>Timelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Launch RFP</td>
<td>DNDi</td>
<td>18 May 2020</td>
</tr>
<tr>
<td>Send back the Intent to Participate letter signed</td>
<td>Service Provider</td>
<td>22 May 2020</td>
</tr>
<tr>
<td>Send the study synopsis to CROs</td>
<td>DNDi</td>
<td>22 May 2020</td>
</tr>
<tr>
<td>Questions sent to DNDi</td>
<td>Service Provider</td>
<td>26 May 2020</td>
</tr>
<tr>
<td>DNDi responses to Q&amp;A</td>
<td>DNDi</td>
<td>29 May 2020</td>
</tr>
<tr>
<td>Reception of proposals</td>
<td>DNDi</td>
<td>12 June 2020</td>
</tr>
<tr>
<td>Notification to Preselected bidders</td>
<td>DNDi</td>
<td>19 June 2020</td>
</tr>
<tr>
<td>Bid Defence Meetings</td>
<td>DNDi / Service Provider</td>
<td>29 June 2020</td>
</tr>
<tr>
<td>Project award</td>
<td>DNDi</td>
<td>06 July 2020</td>
</tr>
<tr>
<td>Full Clinical Trial Agreement Execution</td>
<td>DNDi / Service Provider</td>
<td>31 July 2020</td>
</tr>
</tbody>
</table>

### 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 0 of the RFP.

In order to keep a fair bidding process, questions on the drugs to be assessed will only be answered 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 2.

#### 2.3.2 Confirmation of Intent

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.

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).
<table>
<thead>
<tr>
<th>Questions types</th>
<th>Contact person</th>
<th>Title</th>
<th>Contact information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contractual &amp; Technical aspects</td>
<td>Christophine MARTY</td>
<td>Senior Procurement Manager</td>
<td>15 Chemin Louis Dunant, 1202</td>
</tr>
<tr>
<td></td>
<td>MOREAU</td>
<td></td>
<td>Geneva, Switzerland Phone: +41 22 906 92 61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Email: <a href="mailto:cmarty@dndi.org">cmarty@dndi.org</a></td>
</tr>
</tbody>
</table>

**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 insure quality results.

- **A financial proposal**
  - DNDi Budget template to be completed and attached as Annex 3.
  - 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.

- **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 Company 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 world 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, 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.

To date DNDi has delivered 8 novel treatment to patients suffering from malaria, Leishmaniasis, HAT, pediatric 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/](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 and cutaneous leishmaniasis, the nitro-imidazole DNDI-0690.

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 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), 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-0690 after oral administration of 10 days repeated doses to healthy volunteers.

Pre-clinical package to support Phase I is sufficiently complete to support healthy volunteers’ studies. The Single Ascending Dose study showed a good safety in male and female 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 end of Q4 2020.

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

4.1 Phase I FIH Clinical trial: Key data

Indication: Visceral Leishmaniasis

Study design: Multiple Ascending Dose study in Healthy volunteers and Glomerular Filtration Rate (GFR) assessment

Objective of the study: The overall objective of the study is to assess the safety, tolerability and pharmacokinetic parameters of DNDI-0690

No. of participating countries: 1 country, United Kingdom

Participating clinical sites: 1 site

4.2 Short presentation of the compound

The NCE to be tested will be DNDI-0690. This compound belongs to the nitroimidazole family (7-substituted nitroimidazooxazine) and has the following chemical structure

4.3 General Information on the Phase I MAD study

- Healthy volunteers between the ages of 18 and 60 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, vital signs, medical history, alcohol/drugs of abuse screening, ECG, haematology, chemistry, urinalysis, etc.), serology for: HIV 1/2, HBsAg, and HCV antibody, (see detailed and complete list in the draft synopsis/schedule of events). Standard baseline procedures pre-dosing (e.g. physical examination, vital signs, medical history, alcohol/drugs of abuse screening, ECG, haematology, chemistry, urinalysis etc. ) as well as negative PCR test for COVID-19 at admission.

Standard safety monitoring procedures post-dosing (e.g. AE, vital signs, physical examination, ECG, haematology, chemistry, urinalysis etc.)

❖ **Main Study**

Randomized, double-blind, placebo-controlled, multiple oral administration, ascending dose.

Dosing to start with IMP or placebo in oral Swedish orange capsules (DNDI-0690)

The subjects will be hospitalized in the clinical unit at approximately 6.00 p.m. on Day -4 up to 60h post-dose (Day 12). A follow up visit at Day 17-Day 23 will be done.

<table>
<thead>
<tr>
<th>DNDi-0690</th>
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<tbody>
<tr>
<td>Number of cohorts planned</td>
</tr>
<tr>
<td>Number of subjects/cohort</td>
</tr>
<tr>
<td>Number of subjects planned</td>
</tr>
<tr>
<td>Duration of recruitment</td>
</tr>
</tbody>
</table>
| Duration of dosing | Part A: Moxifloxacin + wash out + 10 days DNDI-0690  
Part B: 10 days DNDI-0690 (iohexol) |
| Duration of Follow up | 7 to 13 days after last dose |

Standard safety monitoring procedures inclusive (e.g. AE, vital signs, ECG, hematology, chemistry, urinalysis etc.)

Specific assessments will be provided with the draft synopsis/schedule of events:

- Central ECG reading by third party
- Troponin I (hypersensitive)
- Creatinine to be evaluated by an enzymatic methodology (colorimetric method not allowed)
- Cystatin C
- Renal Biomarkers in urine samples: NGAL, KIM-1 (optional – to be quoted separately)
- Part A: Holter monitoring for QT assessment will be implemented (central ECG/Holter reading facility already identified) as well as dosing of Moxifloxacin followed by a wash out period prior to dosing of DNDI-0690.
- Part B: GFR assessment following iohexol dosing
❖ **PK sampling**
Plasma, urine and dry blood spots samples to be collected and shipped to a 3rd Party for bioanalysis. Material for dry blood spots (paper collection cards) will be provided by the sponsor. For each subject of 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: Do not store above 25°C - Do not freeze.
- IMP (capsules 200 mg and placebo) will be provided by the Sponsor, packaged in bulk.
- Moxifloxacin and Iohexol will be supplied by the service provider.
- Safety ECG will be read by cohort by a third-party service provider already identified by the sponsor. 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
- 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 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,
• Clinical Trial Monitoring, including supervision of monitoring activities by the service provider Project Manager
• Labelling and shipping of PK samples (frozen) to bioanalysis service provider (based in Europe). Service Provider will prepare the plasma, dry blood spots and urine samples and ship them to a third-party contracted by DNDi for the bioanalysis.
• PK Analysis: Data to be transferred back to the Service Provider for data analysis (interim plasma PK report to be used for the dose escalation decision). The service provider will perform the PK analysis to generate the interim PK reports, including prediction of exposure at the following dose, to support dose-escalation decision.
• Analysis of data from Dry Blood Spot (comparison with Plasma results) - optional
• 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 LPLV) – 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
• Data protection representation and compliance with GDPR, advice of sponsor on legal requirements related to data protection

4.5 Expected reporting
• Study Status Reports (monthly): start-up progress, recruitment, data cleaning
• Meetings: weekly telephone meetings with the sponsor, kick-off meeting, minutes
• Interim Safety Reports (at least 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)
• 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 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:

5.1 Technical criteria
✓ Facilities and license to perform MAD studies in UK
✓ 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 3.
✓ 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, database specifications and edit-checks, Cdisc format
✓ Regulatory and Ethics Committee Approval
✓ Safety Interim Reports / PK Interim Reports (optional)
✓ Periodic study status reports detailed in section 4.2
✓ Monitoring 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 July 2020
Completion of clinical activities is planned in June 2021 or earlier
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: Q&A Form
Annex 3: Budget template
Annex 4: Clinical Trial Agreement template, to be provided at a later stage