Request for Proposal

Clinical Trial Supplies Services
to support a phase 2 clinical trial
in Eumycetoma

Dated: July 2015
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1. PURPOSE

This evaluation is requested by DNDi (Drugs for Neglected Diseases initiative)

DNDi plans to conduct a phase 2 clinical trial to evaluate the efficacy and safety of an investigational new drug compared to Itraconazole in Mycetoma, a serious neglected fungal disease. DNDi is now sourcing a Contract Development and Manufacturing Organization (CDMO) offering pharmaceutical development and manufacturing services.

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 Clinical Trial Supplies Services in support for the conduction of the phase 2 trial.

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 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 this 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>24 July 2015</td>
</tr>
<tr>
<td>Send back the Intent to Participate letter</td>
<td>Service Provider</td>
<td>5 August 2015</td>
</tr>
<tr>
<td>Q&amp;A sent to DNDi Pharm Dev Manager</td>
<td>Service Provider</td>
<td>5 August 2015</td>
</tr>
<tr>
<td>DNDi responses to Q&amp;A</td>
<td>DNDi</td>
<td>12 August 2015</td>
</tr>
<tr>
<td>Reception of proposals</td>
<td>DNDi</td>
<td>26 August 2015</td>
</tr>
<tr>
<td>Notification to pre-selected bidders</td>
<td>DNDi</td>
<td>9 September 2015</td>
</tr>
<tr>
<td>Bid Defense Meetings</td>
<td>DNDi</td>
<td>17 &amp; 18 Sept 2015</td>
</tr>
<tr>
<td>Bidder selection</td>
<td>DNDi</td>
<td>22 September 2015</td>
</tr>
<tr>
<td>Project Start</td>
<td>Service Provider</td>
<td>1 October 2015</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 its questions in writing to the dedicated key contacts identified below. These questions should be submitted to DNDi at the date mentioned in the section 2.2 Timelines of the RFP.

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 2.2 Timelines 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.

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 aspects</td>
<td>Christophine MARTY</td>
<td>Procurement Manager</td>
<td>15 Chemin Louis Dunant</td>
</tr>
<tr>
<td></td>
<td>MOREAU</td>
<td></td>
<td>1202 Geneva Switzerland</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phone: +41 22 906 92 61</td>
</tr>
<tr>
<td>Technical aspects</td>
<td>Béatrice BONNET</td>
<td>Pharmaceutical Development</td>
<td>Phone: +41 22 906 92 25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Manager</td>
<td>Mobile: +41 79 910 74 44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Email: <a href="mailto:cmarty@dndi.org">cmarty@dndi.org</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Email: <a href="mailto:bbonnet@dndi.org">bbonnet@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
  - Acceptance of DNDi Technical Service Agreement template, attached as Annex 4.

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

- A financial proposal
  - Budget template to be completed
- 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, capabilities, 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

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.

The primary objective of DNDi is to deliver a total of 11 to 13 new treatments by 2018 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/](http://www.dndi.org/)

4. SCOPE OF WORK

4.1 Disease background

Mycetoma is a serious neglected fungal disease, caused by a chronic infection of the subcutaneous tissues, mainly in the foot. Infection is most probably acquired by traumatic inoculation of certain fungi or bacteria into the subcutaneous tissue.

Mycetoma commonly effects young adults, (majority males), aged between 20 and 40 years of age, mostly in developing countries. The causative organisms of Mycetoma are distributed worldwide but are endemic in tropical and subtropical areas in the ‘Mycetoma Belt’, which includes the Bolivarian Republic of Venezuela, Chad, Ethiopia, India, Mauritiana, Mexico, Senegal, Somalia, Sudan and Yemen.

Transmission occurs when the causative organism enters the body through a penetrating injury (such as thorn pricks). There is a clear relationship between Mycetoma and individuals who walk barefoot. Patients present to clinic with a painless subcutaneous mass. Mycetoma spreads to involve the skin, deep structures and bone resulting in destruction, deformity and loss of function, which may be fatal. Many patients present late, due to its slow progression and painless nature, and the advance infection may mean amputation is the only treatment.

Current treatment involves a lengthy course of Ketoconazole or Itraconazole followed by surgical removal of the mass and a further course of Ketoconazole/Itraconazole for 6-9 months. The current regimen is expensive, lengthy with a high relapse rate.

This phase 2 clinical study aims to evaluate an investigational new drug versus Itraconazole in terms of efficacy and safety.
4.2 Drugs information

- **Investigational New Product (IND)**
  The IND is a triazole antifungal drug. The IND 102.10 mg capsules and matching placebo will be supplied in bulk via DNDi for clinical packaging and labelling. The capsules are size 3. The recommended storage condition for both IND capsules and IND placebo is “Do not store above 30°C”. The expiry dates for study drugs are currently:
  - IND capsules - October 2017 (to be extended to October 2018 in May 2016)
  - IND placebo - April 2018 (to be extended to April 2019 in May 2016).

- **Itraconazole (ICZ)**
  ICZ is a globally approved triazole antifungal drug, available as 100 mg capsules. The innovator product Sporanox, manufactured by Janssen in Italy, is registered in Sudan. It has a shelf-life of 3 years when stored at temperatures not exceeding 30°C. It is presented as a size 0 capsule, with opaque blue cap and pink transparent body containing coated beads, with commercial markings (see below):

  ![Itraconazole Capsules](image)

  Blinding feasibility studies and manufacture of matching placebo will therefore be required. Blinding feasibility studies for itraconazole should focus initially on over-encapsulation, for example with Capsugel DBcaps® size AAA or AAel.

  The quantities of each dosage form have been estimated below, using a clinical overage of 15%, a minimum manufacturing yield of 85% and a minimum packaging yield of 90%:

<table>
<thead>
<tr>
<th>IMP</th>
<th>Clinical Demand (no overage)</th>
<th>Clinical demand + overage</th>
<th>Gross Demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND Capsule</td>
<td>14580</td>
<td>16767</td>
<td>18630</td>
</tr>
<tr>
<td>IND Placebo</td>
<td>11664</td>
<td>13414</td>
<td>14904</td>
</tr>
<tr>
<td>ICZ Capsule</td>
<td>78624</td>
<td>90418</td>
<td>118193</td>
</tr>
<tr>
<td>ICZ Placebo</td>
<td>157248</td>
<td>180835</td>
<td>236386</td>
</tr>
</tbody>
</table>
4.3 Phase 2 Clinical Trial information

- Indication: Mycetoma
- Study design: Randomized, double-blind, double-dummy study with 3 arms
- Participating country: Sudan 1 site
- Nb of subjects planned: 135 in total (54 in the first 2 arms and 27 in the third)
- This is a three armed study, reducing to 2 arms following intermittent analysis.

<table>
<thead>
<tr>
<th>ARM 1</th>
<th>IND 300 mg</th>
<th>3 x 100 mg IND capsules</th>
<th>4 x 100 mg ICZ placebo</th>
<th>Week 1: Daily dose of 300 mg IND on days 1-3 Weeks 2-52: One weekly dose of 300 mg IND</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM 2</td>
<td>IND 200 mg</td>
<td>2 x IND 100 mg capsules</td>
<td>1 x IND placebo 4 x 100 mg ICZ placebo</td>
<td>Week 1: Daily dose of 200 mg IND on days 1-3 Weeks 2-52: One weekly dose of 200 mg IND</td>
</tr>
<tr>
<td>ARM 3</td>
<td>ICZ 400 mg</td>
<td>3 x IND placebo 4 x 100 mg ICZ capsules</td>
<td></td>
<td>Weeks 1-52: ICZ 200 mg</td>
</tr>
</tbody>
</table>

An interim analysis will be performed after 27 patients have been recruited per arm, and one of the IND arms will then be dropped for efficacy or safety reasons. The remaining IND arm and ICZ arm will resume until 54 patients per arm have been recruited, while patients in the dropped IND arm will be placed on a rescue medication (to be decided) which will most likely be sourced directly in Sudan. The total number of patients in the trial is therefore approximately 135 (i.e. 54 + 54 + 27).

4.4 Clinical Trial Supplies Services

4.4.1 Itraconazole blinding feasibility

- Source sample of Sporanox and other materials (e.g. capsule shells, itraconazole reference standard)
- HPLC method development/adaptation. Please note that an HPLC method for itraconazole API is available in the USP, likewise recommended dissolution conditions are available from US FDA.
- Over-encapsulation study – to include assessment of visual appearance, disintegration, dissolution and need for backfilling.
- Development of matching placebo (e.g. matching capsule containing excipient fill)
- Technical report suitable for clinical trial application purposes.

4.4.2 Itraconazole blinding

- Source required quantity of innovator product (Sporanox) from licensed source with longest possible expiry date and other materials (e.g. capsule shells, excipients, tooling)
- De-blistering (if not possible to obtain bulk capsules, e.g. from Janssen)
• Manufacture (over-encapsulation)
• Quality control testing

Note: This blinding activity assumes that over-encapsulation is feasible.

4.4.3 Itraconazole placebo

• Source required materials (e.g. capsule shells, excipients, tooling)
• Manufacture
• Quality control testing

4.4.4 Packaging, labelling and assembly

• Source packaging materials:
  IND – aluminium foil blisters (specifications available)
  Itraconazole – the commercial packaging for Sporanox is listed as:

  Perfalux tristar blister - plastic foil consisting of 3 layers
  * Polyvinylchloride on the outside;
  * Low density polyethylene in the middle;
  * Polyvinylidene chloride on the inside;
  Aluminium foil (thickness 20 µm) coated on the inner side with colourless heat-seal Lacquer: PVC mixed polymers with acrylates, 6 g/m².
  or:
  PVC blister consisting of -
  Polyvinylchloride 'genotherm' glass clear, thickness 250 µm;
  Aluminium foil (thickness 20µm) coated on the inner side with a colourless heat-seal Lacquer: PVC mixed polymers with acrylates, 6g/m².

• Primary blister packaging/labelling.
• Assembly of blisters into weekly patient kits (e.g. cardboard boxes, wallet cards) containing the required study medication.
• Quality control testing
• QA review and GMP certification

4.4.5 Distribution

• Distribution of supplies to Sudan as two temperature controlled shipments using a qualified shipping agent.
• Logistical support for import/export, customs documentation etc.

Please note:
  o Label text will be provided by DNDi in English and will require translation to Arabic and verification
o Please quote for work packages 2-5 on a per campaign basis. The study is expected to finish in 2018, however it is likely that more than one campaign may be required depending on the exact recruitment rate and the expiry date of supplies.

o Stability studies for blinded ICZ are not included assuming that over-encapsulation is feasible and primary packaging is equivalent to the innovator materials.

4.5 Quality Standards
All operations should be conducted to current Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) standards. A Quality Agreement will be established with DNDi which also reserves the right to audit facilities, procedures and related documentation. For vendors based in the EU, QP certification of clinical trial supplies will be required according to EU GMP Annex 16.

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:

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

- Capacity to deliver
  - Reasonable timelines
  - Project management capabilities
  - Past experience with similar work
  - Profile of staff involved (CVs)

- Financial criteria
  - Realistic costing of the proposal in Euros with NGO rates when possible
6. PROPOSAL REQUIREMENTS, DELIVERABLES & TIMELINES

6.1 Proposals 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 (Activities performed by subcontractors should be clearly indicated)
  
We recommend the use of DNDi template inserted as Annex 3.

- Project Management plan with a detailed description of each activity detailed in section 4.3, plus any underlying assumptions

- Project team involved
- List of tasks and responsibilities
- Project Gantt chart illustrating the timelines for all activities. Please note that DNDi is targeting a study start in Q1 2016

- Feedback on DNDi Technical Service Agreement template
- Any other relevant information

6.2 Deliverables

- Summary updates & technical reports
- Clinical batches of ICZ & ICZ placebo
- Labelled & packaged ICZ, ICZ placebo, IND and IND placebo with appropriate QP certification

6.3 Timelines

Beginning of services planned for Q3 2015
Completion of activities planned for Q2 2017

7. ANNEXES

Annex 1: Intent to Participate letter

Annex 2: Q & A Form

Annex 3: Budget template

Annex 4: Technical Service Agreement template