DNDi
Drugs for Neglected Diseases *initiative*

Request for Proposal

Pharmaceutical Development (Drug Substance & Drug Product) for Visceral Leishmaniasis candidate DNDI-6148

Dated: October 12th 2015

Table of Contents

1. PURPOSE

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

DNDI-6148 is currently being profiled by DND*i* for the treatment of Visceral Leishmaniasis (VL) with the aim to start the First in Human (FIH) study in H1 2017. The compound is now being tested in an exploratory toxicology study, and the aim is to formally nominate it as a preclinical candidate by mid-December 2015.

In order to complete the preclinical activities, DND*i* is now sourcing a Contract Development and Manufacturing Organization (CDMO) offering ideally an integrated platform of pharmaceutical development and manufacturing capabilities to cover both Drug Substance and Drug Product activities.

2. RFP INSTRUCTIONS

2.1. General information

a) DND*i* invites you as a Service Provider to submit one proposal covering process development & GMP API manufacture, clinical supply (formulation development and drug product manufacture) and associated quality controls services.

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 Request for Proposal in no way commits DND*i* to make an award. DND*i* is under no obligation to justify the reasons of its service provider's choice following the competitive bidding. DND*i* could choose not to justify its business decision to the participants of the RFP.

e) DND*i* 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 another 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 DND*i* will consider necessary

f) Late submission proposals are subject to rejection.

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

h) All offers should be submitted in an electronic format.

i) The proposed timelines below indicate the process DND*i* intends to follow. If there are changes to this timelines, DND*i* will notify you in writing.

2.2.Timelines

Process steps	**Responsible party**	**Timelines**
Launch RFP	DND*i*	12 Oct 2015
Send back the Intent to Participate letter	Service Provider	22 Oct 2015
Full Technical Package disclosed to participants	DND*i*	23 Oct 2015
Questions sent to DND*i*	Service Provider	30 Oct 2015
DND*i* responses to questions	DND*i*	13 Nov 2015
Reception of proposals	Service Provider	4 Dec 2015
Bidder Preselection notification*	DND*i*	16 Dec 2015
Bid defense meetings	DND*i*	7 Jan 2016
Project award	DND*i*	12 Jan 2016
Project Start (Drug Substance)	Service Provider	Feb 2016
Project Start (Drug Product)	Service Provider	Jun 2016
Clinical Manufacturing completed	Service Provider	Apr 2017

*****The decision to move forward with preselection will be pending the preclinical candidate nomination meeting scheduled for 15th December 2015.

2.3.RFP processes and contact information

2.3.1. Instructions

All bidders may request further clarifications regarding this RFP by addressing their questions in writing to the dedicated key contacts identified below. These questions should be submitted to DND*i* at the date mentioned in the section 2.2 Timelines of the RFP.

In order to keep a fair bidding process, questions related to this RFP 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 DND*i* 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).

Questions types	**Contact person**	**Title**	**Contact information**
Contractual & Technical aspects	Christophine MARTY MOREAU	Procurement Manager	15 Chemin Louis Dunant 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

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

- A financial proposal

- Budget template for drug substance (Annex 3a) and drug product (Annex 3b) to be completed

- Completed API and Drug Product Manufacturing (IMP) Quality Questionnaires

- High-level comments on the DND*i* template for Pharmaceutical Development Services Agreement

- Administrative information
  - Business Company information: directors and officers, creation date, corporate headquarters, locations, business turnover of the past three 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 DND*i* 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. DND*i* OVERVIEW

3.1. 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, 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.

The primary objective of DND*i* 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, DND*i* aims to bring medical innovation to neglected patients by developing field-adapted treatments.

In doing this, DND*i* 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 DND*i* website: www.dndi.org

4. SCOPE OF WORK

4.1. Drug Substance

DND*i* is requesting proposals for process development activities followed by a cGMP manufacture of 2 kg of API (6 step convergent synthesis). Prior to the GMP manufacture, a demonstration batch on approx. 2 kg will be prepared with the optimized process as a proof of concept. This demonstration batch will be used to initiate formulation development activities and to support preclinical studies.

Within the proposal, the CDMO should evaluate the feasibility and scalability of the route provided by DND*i*, and detail development/optimisation activities (for each step) that have been identified and will be performed as part of this package. The CDMO should also suggest, when appropriate, alternative routes that would be more relevant from a technical, safety and cost-effectiveness points of view.

Additionally, DND*i* requests the CDMO to develop a recrystallisation step on the final stage to get consistent particle size distribution, the desired thermodynamic stable polymorphic form, impurity level and color.

The proposal should also cover process safety assessment, API methods development and validation (for assay & purity, residual solvents and cleaning), forced degradation studies, preparation and qualification of reference standards (for regulatory starting materials, intermediates, key impurities, final API), structure elucidation of reference standard, and ICH stability testing.

4.1.1. API Synthesis: Key data

- 6 step convergent synthesis (performed at 200g scale already) from commercially available starting materials

- No chiral center

4.1.2. List of activities to be performed

Work Package 1: Process Development

1.1. Process development
1.2. Process safety assessment
1.3. Genotoxic Risk Assessment (GRA) of potential impurities in the final API
1.4. Raw materials/reagents purchase to support the demonstration batch manufacture

Work Package 2: Demonstration batch

2.1. Production and analysis of approx. 2 kg of demonstration batch to GLP standard (this batch should be suitable for GLP toxicology studies)

Work Package 3: Analytical support

3.1 Preparation and qualification of reference standards (for regulatory starting materials, intermediates, key impurities and final API)
3.2 Forced degradation studies for API HPLC method
3.3 API methods development and validation for assay & purity, residual solvents and cleaning

Work Package 4: cGMP manufacture and release

4.1. Purchase of raw materials/reagents to support cGMP manufacture
4.2. Production and release of approx. 2 kg of cGMP API

Work Package 5: ICH Compliant Stability program

5.1 ICH stability program (accelerated conditions: 40 °C/75% RH, intermediate condition: 30 °C/65% RH, long term condition: 25 °C/60% RH) for up to 5 years

4.2. Drug Product

DND*i* is requesting the CDMO to carry out formulation development, GMP manufacturing and ICH stability studies for the Phase I clinical supplies: a solid oral dosage form with up to three dose strengths is envisaged, along with matching placebo. Formulation development activities to guide design of a suitable solid oral dosage form for Phase II POC studies will also be included in this proposal.

The compound is characterized by very poor solubility, though showing good oral bioavailability in animal species so far. The formulation development activities for Phase I should therefore focus on simple approaches such as powder in capsule (eg. active only, micronised active, active + wetting agent). The CDMO should nevertheless include an option to develop an alternative prototype formulation for use in the event of poor bioavailability in human. The oral formulation should allow flexibility to explore relatively wide dose range (e.g. from 1 mg to 300 mg) in Phase I (encapsulation). DND*i* recommends the use of a common capsule size, which should allow manufacture of one single placebo size matching all three active strengths.

Non-GMP demonstration batch of API (representative of the API manufacturing process) will be used for formulation development activities and preclinical studies, while the cGMP API batch will be used for clinical supplies manufacturing.

4.2.1. List of activities to be performed

Work Package 1: Phase I-enabling formulation

1.1. Process development for Phase I (powder in capsule): a lead formulation will be selected.
OPTIONAL – Development of an alternative prototype formulation in case of poor bioavailability of the lead

1.2. Manufacture of development batches (max. 2000 units each) from the lead formulation, two dose strengths (lowest and highest) and one matching placebo

1.3. Formal stability studies on development batches: three years, four storage conditions (one month: 50°C/75%RH, six months: 30°C/75%RH and 40°C/75%RH, long term: 25°C/60%RH)

Work Package 2: Solid oral formulation development for Phase Ib/II

2.1 Formulation screening: chemical stability/compatibility for API alone, excipient alone (control), API/excipient combinations and up to four solid oral dosage form prototypes (if excipients are used, preferably on the highest dose strength)

2.2 Formulation development of solid oral dosage form for Phase Ib/II: a lead formulation will be selected.
OPTIONAL - Relative bioavailability study in relevant animal species on the most promising prototype(s) (up to two)

2.3 Manufacture of development batch (max. 2000 units) from the lead formulation, one dose strength

2.4 Formal stability study on development batch: three years, four storage conditions (one month: 50°C/75%RH, six months: 40°C/75%RH, long term: 30°C/75%RH)

Work Package 3: Analytical support for Phase I drug product

3.1 Assay and related substances method development and validation
3.2 Dissolution method development and validation

Work Package 4: Phase I drug product manufacture and clinical supply

4.1 Manufacturing of clinical batches (up to three strengths) plus one matching placebo (max. 2000 units each)
4.2 Clinical packaging for Phase I
4.3 QP release
4.4 Shipment to clinical site
4.5 Clinical stability studies for extreme dose strengths of drug product (bracketing intermediate strength) and matching placebo: three years, two storage conditions (six months: 40°C/75%RH, long term: 25°C/60%RH)

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 DND*i*'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 the GMP manufacture
- Regulatory Inspection outcome
- API Quality questionnaire & Drug Product Manufacturing (IMP) Quality Questionnaire
- Ability to apply appropriate process development and analytical activities suitable to support FIH requirements (fit for purpose)

5.2. Capacity to deliver

- Reasonable timelines
- Project management capabilities
- Past experience with similar work

- 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 which describes:

- General information of the company as described in section 2.4
- Technical information (CMC, Regulatory, Quality) for each part of the project. European guidelines to be followed.
- Budget with full details of your offer including fixed costs and Pass-Through Costs. We recommend the use of DND*i* template inserted as Annex 3.
- Project team involved
- List of tasks and responsibilities
- Project Gantt Chart

6.2. Major deliverables

6.2.1. Drug Substance

- Demonstration batch (2 kg) and cGMP batch (2 kg)
- Certificate of analysis for each batch manufactured (final API and reference standards)
- BSE/TSE statements and GMP certificate
- Process development (including manufacture of demonstration batch) report
- Process safety assessment report
- cGMP campaign report
- Master and executed batch records
- Analytical test procedures, methods validation protocols and reports
- Reference standards and analytical markers characterization report
- Forced degradation study report
- Specifications for API release
- ICH stability protocol, interim and final reports
- Biweekly updates on project progress
- Documentation suitable for IMPD submission

6.2.2. Drug Product

- Clinical batches supply
- Certificate of analysis and statement of cGMP compliance (per batch manufactured)
- TSE statements for excipients
- Formulation development reports
- Executed batch records for DP manufacturing
- Analytical test procedures, methods validation protocols and reports
- Specifications for DP release
- ICH stability protocol, interim and final reports
- Biweekly updates on project progress
- Documentation suitable for IMPD submission

6.3.Terms and Timelines

- All GMP services will be performed under a Quality Agreement
- Beginning of Services planned in February 2016
- Completion of the service (excluding ICH stability) by April 2017
- Clinical trial start in July 2017

6.4.Additional information

After receiving their Intent to Participate letter, DND*i* will provide the bidders with the documentation listed below on both Drug Substance and Drug Product:

- Physical and chemical properties of the API
- Available synthetic route and experimental protocols
- Certificate of analysis of API
- API and Drug Product Manufacturing (IMP) Quality questionnaires
- Pharmaceutical Development Services Agreement template

7. ANNEXES

Annex 1: Intent to Participate letter

Annex 2: Q & A Form

Annex 3: Budget templates for a) drug substance, b) drug product