DNDi
Drugs for Neglected Diseases *initiative*

Request for Proposal

Pharmaceutical Development (Drug Substance & Drug Product) of DNDI-5561 Targeting Visceral Leishmaniasis

Dated: 9 January 2018

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1. PURPOSE

DNDI-5561 compound from aminopyrazole class for the treatment of Visceral Leishmaniasis (VL) has been recently nominated as a preclinical candidate. In order to perform all preclinical activities required to enter into Phase I, DNDi is now sourcing a Contract Development and Manufacturing Organization (CDMO) offering an integrated platform of pharmaceutical development and manufacturing capabilities to cover both aspects of Drug substance and Drug Product activities.

1.1. Visceral Leishmaniasis (VL)

Visceral Leishmaniasis (VL), also known as kala-azar in the Indian sub-continent, is caused by the protozoan parasites Leishmania donovani and Leishmania infantum (= Leishmania chagasii), and is a potentially fatal disease with a worldwide distribution in Asia, East Africa, South America and the Mediterranean region. Visceral leishmaniasis occurs in 80 countries with 300'000 people infected and 40'000 death every year. The parasites are transmitted through the bite of female phlebotomine sand flies and in the human host are obligate intracellular parasites of the reticuloendothelial system, surviving and multiplying in different macrophage populations.

There are a few treatment options available to VL patients:

- Pentavalent antimonials (iv or im) remain the first-line treatment in most parts of the world, except in Bihar State, India where there is a high level of resistance.

- AmBisome™ (iv), an amphotericin B liposome formulation, was shown to have significant activity, even as a single dose treatment, in India

- Oral miltefosine was registered in India in 2002 and is now in Phase IV trials

- Low cost parenteral (im) formulation of paromomycin has completed Phase III clinical trials and was registered in India in 2006, and is in phase III in East Africa.

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 drugs most advanced in development at DND*i* for VL are one in oxaborole and in nitroimidazole classes. It remains essential to add further candidates from different classes to the pipeline to maximise the chance of successfully completing the development of at least one, and preferably two or more drugs to provide a short course, oral treatment.

This lead compound belongs to aminopyrazole class originally from Pfizer. It shows excellent activity in vitro against species of leishmania that cause VL and CL and against strains resistant to existing drugs indicating a novel mechanism of action. This lead compound produces very high levels (up to 100% in some studies) of parasite reduction in both mouse and hamster models of VL and also in two different mouse models of CL

1.2.Aminopyrazole lead compound history

DNDi and Pfizer collaborated on a HTS of the Pfizer Global Diverse Representative Set II which was tested vs. T. Cruzi, T. Brucei & L. Donovani at Institut Pasteur, Korea (IPK) in 2011. VL series 12 (aminopyrazoles) is based on a singleton hit which is a specifically Licensed Material from Pfizer. An agreement between DNDi & Pfizer was signed providing rights for DNDi and partners to develop leads for specified neglected diseases. In June 2014, the first in vivo proof of concept for 2 compounds, from this VL series 12 was achieved. During lead optimization phase, development of the first lead generation of compounds has been stopped due to multiple technical issues including potential a safety risk.

DNDI-5561 was selected as a preclinical candidate from a second generation based on a. 7-day exploratory toxicology study in rats.

2. RFP INSTRUCTIONS

2.1.General information

a) DND*i* invites you as a Service Provider to submit one proposal covering all services described in Section 4.

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 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 timeline, DND*i* will notify you in writing.

2.2.Timelines

Process steps	**Responsible party**	**Timelines**
Launch RFP	DND*i*	09 January 2018
Send back the Intent to Participate letter	Service Provider	15 January 2018
Full Technical Package disclosed to participants	DND*i*	16 January 2018
Questions sent to DND*i*	Service Provider	30 January 2018
DND*i* responses to questions	DND*i*	6 February 2018
Reception of proposals	Service Provider	20 February 2018
Bidder Pre-selection notification	DND*i*	6 March 18
Bid defense meetings (F2F in Geneva)	DND*i*	22 March 18
Project award	DND*i*	26 March 18
Project Start	Service Provider	April 2018

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	Christophine Marty Moreau	Senior Procurement Manager	Phone: +41 22 906 92 61 Email: cmarty@dndi.org
Technical	Andrea Walmsley	Project manager consultant for DND*i*	Email: andreawalmsley4@btinternet.com

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 authorised 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 authorised representative of the company
  - Acceptance of the consultation principles

- 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 DND*i* to assess the opportunity of contracting with your company

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

- A financial proposal
  Budget to be provided for all activities detailed in section 4, the cost breakdown by Work Packages should be respected for DS and DP Services.

- Drug Product Manufacturing and Packaging Quality Questionnaires completed, templates will be provided at a later stage.

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

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 16 to 18 new treatments by 2023 for leishmaniasis, sleeping sickness, Chagas disease, malaria, paediatric HIV, filarial diseases, mycetoma and hepatitis C, 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: http://www.dndi.org/

4. SCOPE OF WORK

4.1.Drug substance

This document is a Request for Proposal for an estimate related to process development of the current route of DNDi compound (9 steps synthesis) followed by cGMP manufacture of ~4 kg. Prior to the GMP manufacture, a demo batch on approx. 4 kg will be prepared as proof of concept with the optimized process. This Demo batch will be used to initiate formulation development activities and to support 4 weeks GLP toxicology studies. Within the proposal, the CDMO should provide feedback as to the scalability of the current route provided, and detail in each step development activities, which have been identified and are needed. If there are specific manipulations which are not feasible for large scale manufacture, these should be discussed in the proposal and alternative methodologies recommended. As a second approach, the CDMO should suggest alternative routes, if they exist, and are considered more viable and discovery route. A comparison of the current route and the alternative approaches should be provided and criteria such as yield, raw materials prices, number of step, critical steps, chemical hazard, simplicity of the work-up, easy purification, crystallization, potential structural alert, etc should be considered. DNDi also requests the CDMO to develop a re-crystallisation step on the final stage to get consistent particle size distribution, the desired polymorphic Form 1, impurity level and color. During the PRD phase, quality/purity of Regulatory Starting Materials (RSM-1) and (RSM-2) should be determined/evaluated to prevent negative impact on the downstream chemistry.

This proposal is not limited to GMP manufacture but should also cover Process safety assessment, salt and polymorph screening, API Methods development and validation (for assay&purity, chiral purity, residual solvent and cleaning), forced degradation studies, preparation and qualification of reference standards for RSM (Regulatory Starting Material), intermediates and final API and analytical markers and ICH stability testing.

4.1.1. API Synthesis: Key data

- 9 steps synthesis already performed up to 50g from chiral and commercial available starting materials– 1 chiral center
- No racemization during the synthesis
- Chiral center introduced by chiral starting material
- Several intermediates purified by silica gel column chromatography
- Several protection/deprotection steps

4.1.2. List of activities to be performed

Work Package 1 (process research and development)	
1.1	Route scouting
1.2	Process Development of the selected route
1.3	Reactive Crystallization Development
1.4	Process safety assessment
1.5	Genotox Risk Assessment (GRA) of manufacturing process: ID all potential genotoxins in API
1.6	Salt and polymorph screens on selected API form
Work Package 2 (Demonstration batch)	
2.2	Purchase of raw materials/reagents to support demonstration batch manufacture (non-GMP)
2.1	Production of 4Kg Demonstration Batch (non-GMP) with CoA
Work Package 3 (GMP API manufacture)	
3.2	Purchase of raw materials/reagents to support cGMP API manufacture
3.2	Production of 4 kg cGMP API with CoA, BSE/TSE
3.3	QC release testing including GMP Certificate of Analysis and QP release
Work Package 4 (Analytical methods development and qualification)	
4.1	API Methods development and qualification (for assay&purity, chiral purity, residual solvent and cleaning) to comply with the Phase I regulatory Requirements (EU)
4.2	Forced degradation studies for API HPLC method
4.3	Preparation and qualification of reference standards for RSM (Regulatory Starting Material), intermediates and final API

4.4	Preparation and qualification of analytical markers (impurity samples for RSM, intermediates and final API)
Work Package 5 (Stability studies)	
5.1	Stability program (25°C/60%RH, 30°C/75%RH, 40°C/75%RH) up to 5 years (last two years being optional)
Work Package 6 (Stable Isotopically Labelled (SIL) synthesis)	
6.1	Stable Isotopically Labelled (Deuterated) synthesis (1.5g) to support bioanalytical method development, including a Certificate of Analysis

4.2. Drug Product

Oral bioavailability of BCS class II drugs having a poor water solubility and reasonable permeability is often limited by the drug dissolution step from the drug product. Thus, to support FIH, formulation development activities should be focused preferably on bioavailability enhancing methods such as:

- Salt formation
- Micronization and nanomilling with/without surfactant (to investigate the increasing of wettable surface area, size reduction without affecting the solid state (crystalline)

The most promising formulation strategy will be taken forward into the development and manufacturing phase.

Further refinement of the formulation used for toxicology studies and process development will be needed to design appropriate oral dosage form for Phase I/II POC study. Such oral formulation should allow flexibility to explore relatively wide dose range (e.g. from 1mg to 300mg) in Phase I (Encapsulation), and guide design of suitable dosage form for Phase II POC studies (Tableting).

4.2.1. List of activities to be performed

Work Package 1 (Pre-formulation)	
1.1	Chemical stability/compatibility will be evaluated by storage of the API alone, excipient alone, API/Excipient combinations, up to 4 capsules formulation prototypes generation (preferably on the highest dose strength) and short-term stability studies to help in the section of formulations allowing further development studies.
1.2	Relative Bioavailability Study in dog (optional) on the most promising prototype(s) (up to 2) with reference formulation
Work Package 2 (Formulation for non-GLP safety/toxicology package)	
2.1	Process development to support oral formulation suitable for toxicology studies
2.2	Manufacture of a formulation for non-GLP toxicology studies with CoA Batch size: formulation containing 0.5-1Kg API
	Supportive stability studies (up to 6 months) for shelf-life assignment
2.3	In-use stability study
Work Package 3 (Formulation for GLP safety/toxicology package)	
3.1	Manufacture of a formulation for GLP toxicology studies with GMP like CoA Batch size: formulation containing 2.5Kg API
	Supportive stability studies (up to 6 months) for shelf-life assignment
3.2	In-use stability study
Work Package 4 (Further formulation development for Phase I)	
4.1	Formulation refinement
	Development/Stability batch (~1-2kg) may be carried out on equipment intended for manufacture of Clinical batches Batches size will be as follows: Up to 2 formulations * 2 dose strengths (lowest and highest) – 1 matching placebo
4.2	Formal stability studies on up to two Development batches (three dose strengths) with one matching placebo. Study duration three years, four storage conditions (25°C/60%RH, 30°C/75%RH optional, 40°C/75%RH, 50°C/75%RH)
Work Package 5 (Analytical method development and qualification)	
5.1	Assay and Related Substances Method (Accuracy, linearity and system precision, Method repeatability, Limits of detection and quantification (LOD and LOQ), Specificity and Solution stability)

5.2	Dissolution Method (Accuracy, linearity, system precision, specificity and filter compatibility, Solution stability and Method repeatability)
Work Package 6 (Clinical batches manufacture Phase I)	
6.1	Manufacturing of clinical batch (capsules, 3 dose strengths, max 3,000 units each) + matching placebo
6.2	Packaging (bottles) for Phase I Labelling for the clinical trials (2 languages)
6.3	QP release for the clinical use
6.4	Shipment to the single clinical site (in Europe)
Work Package 7 (Stability studies on clinical batches)	
7.1	Formal stability studies on up to two Development batches (three dose strengths) with one matching placebo. Study duration five years (last two years optional), four storage conditions (25°C/60%RH, 30°C/75%RH optional, 40°C/75%RH, 50°C/75%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 total cost of the offer.
Proposals will be assessed against the main following criteria but not limited to:

5.1.Technical criteria

- Ability to apply appropriate process development and analytical activities suitable to support FIH requirements (fit for purpose)
- The CDMO will have the capability and experience/expertise to perform all the activities in a licensed facility at the scale outlined in paragraph 1.2.
- DND*i* is looking for a CDMO that has renowned credentials in running successful development projects for small organizations.
- Track records with regulatory bodies and regulatory inspections outcome

5.2.Capacity to deliver

- DND*i* would like to work in partnership with the CDMO and expects the CDMO to provide strong intellectual input and ownership on the project.
- Project management expertise, responsiveness from various business units, clear and open communication channels as well as on-time and on-budget delivery are expected. A single point of contact for project management with senior experience will need to be appointed
- Past positive experience with similar activities/scale

5.3.Financial criteria

- Realistic costing of the proposal with NGO rates whenever 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
- Complete scope of work description, with a full list of activities (CMC, Regulatory, Quality) to be performed for each work package of the project.
- Budget with full details of your offer including fixed costs and Pass-Through Costs, clearly broken down by Work Packages for DS and DP Services.
- Project team involved
- List of tasks and responsibilities
- Realistic project Gantt Chart detailing the project schedule from start to finish, including multiple options if appropriate.
- Any other relevant information

6.2.Terms and Timelines

- All services will be performed under a Quality Agreement
- Beginning of Services planned in April 2018
- Timelines for each activity subset should be clearly defined
- Completion of the service (including 12 months ICH stability data on the tablet) in July 2019 at the latest.

6.3.Additional information

After receiving their Intent to Participate letter, DND*i* will provide the bidders with the documentation listed below:

- Safety information (MSDS)
- 50g discovery route protocol and CoA
- Preformulation report
- Full details of work packages and deliverables
- Drug Product Manufacturing (IMP) and Packaging Quality questionnaires
- Pharmaceutical Development Services Agreement template

7. ANNEXES

Annex 1: Intent to Participate letter

Annex 2: Q & A Form