

Request for Proposal

DNDI-6174 **CTA-enabling package**

Dated: June 28th, 2021

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1. PURPOSE

DNDI-6174 is a new NCE (New Chemical Entity) nominated by DNDi as a preclinical candidate as specific treatment for leishmaniasis. In partnership with Eisai and funded by GHIT (Global Health Innovative Technology Fund), the aim of this project is to demonstrate the suitability of DNDI-6174 for progression to clinical Phase I.

The objective of this proposal is to complete CTA-enabling preclinical safety package taking into consideration the following points:

- Work that has already been done (see Compound Information), and especially a 14-day toxicity study in the rat.
- Timelines for initiation of enabling toxicology studies is end of October 2021:
 - Preliminary activities: nonclinical oral formulation development followed by PK assessment in rat and dog to start early November 2021 at the latest.
 - Ultimate study on the critical path: 28-day toxicity study in the dog.
 - Completion of preclinical package (audited draft reports, at minimum): December 2022.
 - Clinical candidate nomination for Phase 1: February 2023.
 - Initiation of Phase 1 Q1 2023
- Dog as the non-rodent species.
- An appropriate Project Management approach where all activities/studies will be performed, analyzed, and discussed in an integrated manner with the Sponsor.
- DNDi and DNDi donors in general are requiring particular care to animal welfare and use the NC3RS as advisor body. For this purpose and if not done yet, we are encouraging all applicants to familiarize with the various guidelines and requirements by the NC3Rs website and take note of the recommendations we will follow for selecting an appropriate contractor (see Annex 4).
- Clinical Phase I will be conducted in Europe.

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 DNDI-6174 CTA-enabling preclinical package.
- 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.
- j. If there are changes to this timeline, DNDi will notify you in writing

2.2 Timelines

Process steps	Responsible party	Timelines
Launch RFP	DNDi	June 28 th 2021
Send back the Intent to participate	Service Provider	July 5 th 2021
Questions sent to DNDi	Service Provider	July 5 th 2021
DNDi responses to Questions	DNDi	July 12 th 2021
Proposal submission	Service Provider	August 2 nd 2021
Bidder preselection notification	DNDi	August 11 th 2021
Bid defense meeting (if selected)	DNDi / Provider	August 17 th 2021
Project award	DNDi	August 27 th 2021
Project start	Service Provider	October 2021

2.3 RFP processes and contact information

2.3.1 Confirmation of Intent

Please transmit your intent to participate by using and signing the document attached in Annex 1 (with no redline please). 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 (contact details below).

Please note the “intent of 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 experiences working with services providers and contains widely acceptable terms in RFP.

2.3.2 Questions

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.

To submit your questions, please use the form attached as Annex 2.

Topics	Contact person	Title	Contact information
Contractual & Business aspects	Christophine MARTY-MOREAU	Senior Procurement Manager	15 Chemin Camille-Vidart, 1202 Geneva, Switzerland Phone: +41 22 906 92 61 Email: cmarty@dndi.org
Study design and conduct	Stéphanie BRAILLARD	NonClinical Development Senior Manager	15 Chemin Camille-Vidart, 1202 Geneva, Switzerland Phone: +41 22 906 92 24 Email: sbrailard@dndi.org

2.4 Format and content of the proposal

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

1. 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.

2. Company profile
 - History, locations and management.
 - Key figures: headcounts and revenue of the past 3 years (global and in the field of service provided).
 - General services provided and capabilities.
 - Customer's reference.
 - Any other relevant information enabling DNDi to assess the opportunity of contracting with your company, for example previous experience in meeting the above requirements for implementation of the 3Rs.

3. A technical proposal

Detailed proposal explaining how your company's approach will enable DNDi team to meet project timelines and ensure quality results:

- Activities list, including outline study plans, and any study design considerations.
- Timing (initiation, experimental phase, draft report for each activity), possibly with a

- draft Gantt chart
 - Answers to the NC3Rs standard question about the use of dogs (Annex 5).
4. A financial proposal
- A comprehensive budget for each of the 14 activities detailed in section 4.2 with Direct and Pass Through Costs.

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 organisation.

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 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, 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/>

4. SCOPE OF WORK

4.1 Compound information

DNDI-6174 is a small organic compound that showed excellent *in vitro* and *in vivo* (mouse and hamster model) efficacy against various strains of leishmania parasites. It displays pharmacological and physico-chemical properties consistent with DNDi Target Product Profile and will be developed as an oral treatment of maximum 14 days, ideally in combo therapy with another NCE.

Preliminary safety and toxicology assessment also demonstrated a promising safety profile:

- Negative in mini-AMES, Micronucleus CHO-cells and MLA (non-GLP)
- In silico prediction of QT prolongation, but cardiomyocytes assay (hiPSc-CM MEA) with no physiologically significant field potential prolongation.
- hERG patch clamp study: >30 μ M as IC50
- No significant alert in Safety screen panels.
- 3T3 NRU Phototoxicity assay: clean.
- Potential for mitochondrial toxicity de-risked with several *in vitro* assays (biochemistry assay, MitoExpress and Seahorse)
- 14-day toxicity study in the rat: NOAEL identified at 80 mg/kg. Initial observations made on liver, thyroid, lymphoid organ and genital tract.

ADME and DDI profile of DNDI-6174 was evaluated in the following experiments:

- Stability in liver microsomes and hepatocytes, various species including rat and dog.
- Metabolites identification done from microsomes (human, rat, and dog), and rat plasma samples: No major metabolite, no reactive metabolite and metabolites identified in human microsomes covered by rat and dog.
- Protein binding, various species including rat and dog.
- Blood-to-plasma ratio and plasma stability (several species, including rat).
- PK PO in Mouse, Hamster, Rat and Dog
- PK IV in Mouse, Rat and Dog
- CYP induction: no signal in transcriptional activation assays.
- CYP inhibition: Time Dependent Inhibition of 2D6 and 3A4. No significant inhibition of 2C9, 2C19, and low inhibition of 1A2.
- High potency inhibition of MATE-1, no significant inhibition of BCRP, BSEP, OAT1, OAT3 and OCT1, OCT2, OATP1B1, OATP1B3, MATE2-K.
- Preliminary Human dose prediction estimation: 10 to 50 mg/day.

Regarding analytical methods, a fit-for-purpose bioanalytical (BA) method (LC-MS/MS) was developed for rat, dog, hamster, and mouse plasma.

The following characteristics of DNDI-6174 are important and are to be considered for

developing a suitable proposal.

- Oral administration
- Limited solubility, good permeability, and acceptable bioavailability.
- A free form of API was used so far, and a salt is under development with the aim to improve solubility. This salt will have to be used for the preclinical package.

4.2 Activities

ID	Title	Species	Description/notes
1	Development of a suitable oral formulation for <i>in vivo</i> nonclinical studies	Rat and Dog	A single oral suspension is needed for rats and the dogs and will be used during PK, safety pharmacology and toxicity studies (CTA enabling package and further nonclinical studies). Targeted concentration: ≥ 100 mg/mL, with a minimal stability of one week
2	PK studies	Rat and Dog	Goal is to check and validate the exposure following the administration of DNDI-6174 (new form) with the new developed formulation (cf activity 1) Several doses to assess linearity and anticipate accumulation, if any. Fit-for-purpose analytical methods can be used for quantifying DNDI-6174 in plasma and in formulation.
3	Bioanalytical Method development and validation.	Rat plasma	GLP. To validate a method for DNDI-6174 quantification in rat plasma that will be used during GLP studies. Including long term stability (6 months).
4	Bioanalytical Method development and validation.	Dog plasma	To validate a method for DNDI-6174 quantification in dog plasma that will be used during GLP studies. Including long term stability (6 months). GLP.
5	Dose formulation Method development and validation		GLP. To validate a method for the formulation that will be used during GLP rat and dog studies, and <i>in vitro</i> genotoxicity studies.

6	DRF and 7-day toxicity study.	Dog	Non-GLP. Including bioanalysis and TK. Including ECG with jackets on day 1. Including histopathology on abbreviated list of tissues (liver, lung, heart, brain, spleen, eye and skeletal muscle (thigh and diaphragm))
7	28-day repeat dose oral toxicity study with a 28- day recovery period.	Rat	GLP. Use of sexually mature animals. Including <i>in vivo</i> Micronucleus test. Including Irwin test- one gender Including Respiratory function – the other gender. Including DFA, bioanalysis and TK. Including collection of plasma samples for potential metabolites identification. Options: endpoints for assessing possible mitochondrial toxicity.
8	28-day repeat dose oral toxicity study with a 28- day recovery period.	Dog	GLP. Use of sexually mature animals. Including DFA, bioanalysis and TK. Including collection of plasma samples for potential metabolites identification.
9	Bacterial Mutation Assay (Ames assay)	<i>In vitro</i>	GLP. Including dose formulation analysis.
10	Chromosomal aberration.	<i>In vitro</i>	GLP. Human peripheral blood lymphocytes. Including dose formulation analysis.
11	hERG,	<i>In vitro</i>	GLP. HEK293 cells. Physiological temperature Including dose formulation analysis.
12	CV Telemetry study	Dog	GLP. Including DFA. Optional: a few TK timepoints and bioanalysis.

DNDi

Drugs for Neglected Diseases initiative

13	Identification of circulating metabolites from plasma	Rat and Dog	Non-GLP. As an option.
14	Drafting of nonclinical summaries for regulatory submissions	na	e.g. CTA, NDA under CTD format. As an option.

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, customer tailoring 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 fitting with our requirements.
 - Project management capabilities.
 - Willingness to work together in a partnership mode.
 - Ability to conduct all activities (avoiding as much as possible outsourcing of activities).
 - Past experience with similar work.
- **Ethical criteria**
 - Ability to comply as much as possible with the principles of UK legislation regarding animal use.
 - Outline protocols including propositions for implementing the 3Rs, such as efficient study design to reduce animal numbers, microsampling, social housing, extended enrichment programs, etc.
- **Financial criteria**
 - Realistic costing of the proposal

6. PROPOSAL REQUIREMENTS, DELIVERABLES & TIMELINES

6.1 Proposals requirements

Please refer to section 2.4 regarding detailed proposals requirements. Please make sure that the reader can easily make the link between activity scope, timelines and costs

6.2 Deliverables

- Protocols (outlines to be provided within proposal).
- Draft study reports for each experiment/study provided to DNDi maximum 4 weeks after the end of the experimental phase.
- Final reports
- Technical, scientific, and regulatory advice through the length of the project.

6.3 Timelines

- Availability of API for formulation development and PK studies (activities 1 and 2, potentially initiation of activities 3, 4 and 5): early October 2021.
- Beginning of services planned in October 2021.
- Availability of API for activities 3 to 14: end of February 2022.
- Completion of preclinical package (audited draft reports, at minimum): November 2022.

6.4 Additional information

- DNDi will provide in due course the API in needed quantities, as well as available data if required.
- SLIS (internal standard) will also be provided for Bioanalytical methods.

7. ANNEXES

Annex 1: Intent to Participate letter

Annex 2: Q&A Form

Annex 3: Booklet: Choosing contractors for animal research

Annex 4: NC3Rs standard questions about the use of dogs