DNDi
Drugs for Neglected Diseases *initiative*

DNDI-8525 & DNDI-8526
14-day toxicity study in rat and dog
Request for Proposal

DND*i* contacts:

Procurement: Christophine Marty-Moreau, Senior Procurement Manager
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Science: Fanny Escudié, Discovery Project Manager
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Eric Chatelain, Head of Drug Discovery
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1. PURPOSE

DNDI-8525 and DNDI-8526 are New Chemical Entities (NCEs) selected by DND*i* as optimized leads for treating visceral leishmaniasis. In partnership with Takeda and funded by GHIT (Global Health Innovative Technology Fund), the aim of this project is to demonstrate the suitability of one or two compounds for progression to pre-clinical candidate nomination. Non-GLP exploratory toxicology studies with these 2 compounds are therefore planned to finalize the nomination package.

The objective of this proposal is to complete a Dose Range Finding study (DRF) followed by a 14-day exploratory study in rat and dog under non-GLP conditions.

2. Request For Proposal (RFP) INSTRUCTIONS

2.1 General information

2.1.1 DND*i* invites you as a Service Provider to submit a proposal with regards to this RFP for DNDI-8525 and DNDI-8526 DRF and 14-day exploratory toxicity study in rat and dog.

2.1.2 This entire RFP and all 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.

2.1.3 All bidders are required to complete and send in return the Intent to Participate letter

2.1.4 The issuance of this current 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.

2.1.5 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 other proposals 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.

2.1.6 Late submission proposals are subject to rejection.

2.1.7 DND*i* 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.

2.1.8 All offers should be submitted in an electronic format.

2.1.9 A proposed time plan set out below indicates the process DND*i* intends to follow.

2.1.10 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*	March 29th 2022
Intent to participate letter	Service Provider	April 5th 2022
Questions	Service Provider	April 5th 2022
Responses	DND*i*	April 8th 2022
Proposal submissions	Service Provider	April 22nd 2022
Bidder preselection notification	DND*i*	May 2nd 2022
Bid defense meeting (if selected)	Service Provider/DND*i*	May 9th 2022
Project award	DND*i*	May 20th 2022
Agreement signed	Service Provider/DND*i*	July 2022
Project start	Service Provider	At the latest September 1st 2022
Project end (draft report received by DND*i*)	Service Provider	At the latest end March 2023

2.3 RFP processes and contact information

2.3.1 Confirmation of intent

Please forward your intent to participate by using and signing the document attached in Annex 1 (with no redline please). 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 (contact details below).
Please note the "intent to participate letter" is a standard document which DND*i* 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 for RFP.

2.3.2 Questions

All bidders may request further clarifications with regards to 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 P: + 41 22 906 92 61| cmarty@dndi.org
Study design and conduct	Fanny ESCUDIE	Discovery Project manager	15 Chemin Camille-Vidart | 1202 Geneva | Switzerland P: +41 22 555 19 54 | fescudie@dndi.org
Study design and conduct	Eric CHATELAIN	Head of Drug Discovery	15 Chemin Camille-Vidart | 1202 Geneva | Switzerland T: +41 (0)22 906 92 63 | M: +41 (0)79 321 54 43 | echatelain@dndi.org

2.4 Format and content of the proposal

Answers 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 DND*i* to assess the opportunity of contracting with your company, for example previous experience in meeting the above requirements for implementation of the 3Rs (The 3Rs | NC3Rs) or similar

3. A technical 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 4)

4. A financial proposal
- A comprehensive budget for each of the 8 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 for 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, DND*i* is a collaborative, patient's needs driven, not for profit drug R&D organisation. 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 Compound information

DNDI-8525 and DNDI-8526 are small organic compounds with an identified mechanism of action that are showing excellent *in vitro* and *in vivo* (hamster model of VL infection) efficacy against various strains of *leishmania* parasites. It displays pharmacological and physico-chemical properties consistent with DND*i* Target Product Profile (TCP) and will be developed as an oral treatment of maximum 14 days, ideally in combination therapy with another NCE.

Preliminary safety and tolerability assessment have demonstrated so far promising safety profiles for these 2 compounds; in short:

- No genotoxicity: Negative in mini-AMES, Micronucleus CHO-cells (non-GLP)
- No cardiac signals: IC_{50} >30 µM in hERG patch clamp study
- No significant safety alert signals in pharmacologically relevant receptors and enzymes screen panels

ADME profile of DNDI-8525 and DNDI-8526 were evaluated in the following experiments:

- Stability in liver microsomes and hepatocytes, various species including rat and dog
- Metabolites identification in human hepatocytes
- Protein binding, various species including rat and dog
- Blood-to-plasma ratio and plasma stability (several species, including dog)
- PK PO in Mouse, Hamster, Rat and Dog – formulation for oral dosing is known
- PK IV in Mouse, Hamster, Rat and Dog – formulation for IV dosing is known
- CYP inhibition: No significant inhibition of 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4

Regarding analytical methods, a fit-for-purpose bioanalytical (BA) method (LC-MS/MS) was developed for rat and dog plasma.
Dose formulation was checked by HPLC system (fit-for-purpose, too).

The following characteristics of DNDI-8525 and DNDI-8526 are important and are to be considered for developing a suitable proposal.

- Oral administration
- Limited solubility, good permeability, and acceptable bioavailability
- A free form (base) of the APIs was used so far, and salts are under consideration with the aim to potentially improve solubility and bioavailability. Salt forms of the compounds will be used for the preclinical package if superior exposure is demonstrated as compared with the free base.

4.2 Activities

The list of activities depicted below are foreseen for each of the following compounds:

- DNDI-8525
- DNDI-8526

ID	Title	Species	Description/notes
1.1	Dose range finding (DRF)/ Maximum tolerated dose (MTD)	Rat	Non-GLP
1.2	14-day repeated oral toxicity study For both compounds, DNDI-8525 and DNDI-8526	Rat	14-day non-GLP study including bioanalysis and toxicokinetics (TK) at day 1 and day 14. Including histopathology on abbreviated list of tissues (liver, lung, heart, brain, spleen and skeletal muscle (thigh and diaphragm)); list non exhaustive and to be adjusted accordingly if necessarily
2.1	Dose range finding (DRF)/ Maximum tolerated dose (MTD)	Dog	Non-GLP
2.2	14-day repeated oral toxicity study For both compounds, DNDI-8525 and DNDI-8526	Dog	14-day non-GLP study including bioanalysis and toxicokinetics (TK) at day 1 and day 14. Including histopathology on abbreviated list of tissues (liver, lung, heart, brain, spleen and skeletal muscle (thigh and diaphragm)); list non exhaustive and to be adjusted accordingly if necessarily
3	Bioanalytical Method transfer and validation	Rat plasma	Non-GLP To validate (transfer validation) a method for DNDI-8525 & DNDI-8526 quantification in rat plasma that will be used during the studies
4	Bioanalytical Method transfer and validation	Dog Plasma	Non-GLP To validate (transfer validation) a method for DNDI-8525 & DNDI-8526 quantification in dog plasma that will be used during the studies
5	Dose formulation method transfer validation		Non-GLP To validate a method for the formulation that will be used during GLP rat and dog studies
6 Optional	*Identification of circulating metabolites from plasma*	*Rat and Dog*	*Non-GLP* *Samples to be stored until decision*

4.2.1 Description of activities

- **Dose range finding (DRF)/MTD in each species (rats and dogs)**

GLP Status: non-regulated

Purpose of the study: DRF / MTD: The DRF in rats and dogs will aim at finding the dose that will produce tolerable levels of adverse toxic effects of the 2 tested

	compounds. Adverse effects of acute doses administration (single dose escalation) will be determined. Data from this phase will assist in estimating the maximum tolerated dose for a single administration and establish doses for a repeat dose phase
Route of Administration	Oral (gastric gavage)
Frequency	Single dose escalation till MTD
Animal species/Breed	Sprague-Dawley Rat. Males and females; Beagle dogs. Males and females
In vivo observations	Clinical signs and mortality, body weight food consumption
Toxicokinetic	Blood samples collection from satellite rat or dog/sex/dose, predose and up to 24 hours after dosing. Plasma aliquots stored at –80°C till analysis

- **14-day repeated oral toxicity study in rat (non-GLP)**

GLP Status	non-regulated
Purpose of the study	To investigate toxicity induced by the test article when administered daily for 14 consecutive days. To define a NOEL and NOAEL. Is considered as a de-risking study before moving to a GLP 28-day toxicity study in rat pending preclinical candidate nomination
Route of Administration	Oral (gastric gavage)
Frequency	Once daily (14 days)
Animal species/Breed	Sprague-Dawley Rat. Males and females
Groups	3 doses, plus vehicle / 5 animals/sex/group.. Tentative doses- to be confirmed; to be determined following DRF
In vivo observations	Clinical signs and mortality, body weight food consumption
Clinical Pathology	Hematology, Clinical Chemistry and urinalysis at the end of treatment period (standard parameters) – all rats
Pathology	Macroscopic examination of main/altered organs, collection, and fixation for possible histological examination
Microscopic evaluation	All tissues from the control and high dose groups will be processed to slides and evaluated If any test-related findings are found in the high dose group, mid and low dose groups will be assessed sequentially

Toxicokinetic	Blood samples collection from satellite rats/sex/dose, predose and up to 24 hours after dosing on Day 1. As well as predose and up to 48 hours on day 14. Plasma aliquots stored at –80°C till analysis

- **14-day repeated oral toxicity study in dog (non-GLP)**

GLP Status	non-regulated
Purpose of the study	To investigate toxicity induced by the test article when administereddaily for 14 consecutive days To define a NOEL and NOAEL Is considered as a de-risking study before moving to a GLP 28-day toxicity study in dog
Route of Administration	Oral (gastric gavage)
Frequency	Once daily (14 days)
Animal species/Breed	Beagle dogs. Males and females
Groups	3 doses, plus vehicle/ 3 animals/sex/group. Tentative doses- to be confirmed; to be determined following DRF
In vivo observations	Clinical signs and mortality, body weight food consumption
Clinical Pathology	Hematology, Clinical Chemistry and urinalysis at the end of treatment period (standard parameters) – all rats
Pathology	Macroscopic examination of main/altered organs, collection, and fixation for possible histological examination
Microscopic evaluation	All tissues from the control and high dose groups will be processed to slides and evaluated If any test-related findings are found in the high dose group, mid and low dose groups will be assessed sequentially
Toxicokinetic	Blood samples collection from satellite dogs/sex/dose, predose and up to 24 hours after dosing on Day 1. As well as predose and up to 48 hours on day 14. Plasma aliquots stored at –80°C till analysis

- **Bionanalytical Method Transfer and validation (non-GLP)**

Purpose of the study	Transfer and validation of a BA method for quantifying the test items DNDI-8525 and DNDI-8526. Will be used to quantify the test items in plasma samples collected during the 14-day toxicity study
Technique	LC-MS/MS
Matrix	Rat plasma and dog plasma

- **Dose Formulation Method Transfer and validation (non GLP)**

Purpose of the study	Transfer and validation of existing method. Will be used to quantify the test items DNDI-8525 and DNDI-8526 in dose formulation during the 14-day toxicity study
Technique	LC-UV

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:

- 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.

6.2 Deliverables

- Protocols (outlines to be provided within proposal)
- Draft study reports for each experiment/study provided to DND*i* 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 foreseen by July 15th 2022
- Beginning of services planned in September 2022
- Completion of preclinical package (draft reports, at minimum): by mid/end March 2023

6.4 Additional information

- DND*i* will provide the API in needed quantities, as well as available data if required

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