Request for Proposal

CC6166
CTA-enabling preclinical package

Dated: December 1st, 2020
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1. PURPOSE

CC6166 is a new NCE (New Chemical Entity) nominated by DNDi as a preclinical candidate as specific macrofilaricide treatment for Onchocerciasis.

The aim of this project is to demonstrate the suitability of CC6166 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 and a 7-day toxicity study in the dog.
- Timelines for initiation of enabling toxicology studies is August 2021 and notably:
  - Clinical candidate nomination for Phase 1 Q3 2022
  - 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.
- Clinical Phase I will be performed in Europe or Africa
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 CC6166 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. If there are changes to this timeline, 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>Dec 1st, 2020</td>
</tr>
<tr>
<td>Send back the Intent to participate</td>
<td>Service provider</td>
<td>Dec 4th, 2020</td>
</tr>
<tr>
<td>Questions sent to DNDi</td>
<td>Service provider</td>
<td>Dec 4th, 2020</td>
</tr>
<tr>
<td>DNDi responses to Q&amp;A</td>
<td>DNDi</td>
<td>Dec 7th, 2020</td>
</tr>
<tr>
<td>Proposal submission</td>
<td>Service Provider</td>
<td>Dec 14th, 2020</td>
</tr>
<tr>
<td>Bid defense meeting (if any)</td>
<td>DNDi</td>
<td>w/o Dec 14th 2020</td>
</tr>
<tr>
<td>Project award</td>
<td>DNDi</td>
<td>Early Jan 2021</td>
</tr>
<tr>
<td>Project start</td>
<td>Service provider</td>
<td>Upon budget/funding approval (Q3 2021)</td>
</tr>
</tbody>
</table>

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 Olivier Degodet (contact details below).

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.

<table>
<thead>
<tr>
<th>Topics</th>
<th>Contact person</th>
<th>Title</th>
<th>Contact information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contractual &amp; Business</td>
<td>Olivier DEGODET</td>
<td>Senior Procurement</td>
<td>15 Chemin Louis Dunant, 1202</td>
</tr>
<tr>
<td>aspects</td>
<td></td>
<td>Manager</td>
<td>Geneva, Switzerland</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phone: +41 22 555 1911</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Email: <a href="mailto:odegodet@dndi.org">odegodet@dndi.org</a></td>
</tr>
<tr>
<td>Study design and conduct</td>
<td>Ivan SCANDALE</td>
<td>Sr Project Manager,</td>
<td>15 Chemin Louis Dunant, 1202</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discovery</td>
<td>Geneva, Switzerland</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Email: <a href="mailto:iscandale@dndi.org">iscandale@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

- 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

- 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, attached as Annex 3 to be completed

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

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 patients (e.g. malaria, paediatric HIV, filarial infections) and development of diagnostics and/or vaccines 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

CC6166 is a small organic compound that showed in vitro efficacy against Onchocerca volvulus and several others filarial species. CC6166 also showed efficacy in vivo (5 to 10 days twice daily administration in jBalb/C infected with *L. sigmodontis*). It displays pharmacological and physico-chemical properties consistent with DNDi Target Product Profile.

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

- Negative in mini AMES test (5 strains)
- Negative in vitro micronucleus with and without S9 fraction activation
- hERG patch clamp study: >30 µM as IC₅₀
- CERP Panel, channels, and enzymes: 1 significant binding at 10 mM (>50%)
- 14-day tox study in the rat: NOAEL identified
- MTD and 7- Day tox study in the dog: NOAEL not identified

DMPK profile of CC6166 was evaluated in the following experiments:

- Stability in liver microsomes and hepatocytes, various species including rat and dog.
- Metabolites identification done from microsomes, hepatocytes study (human, rat, and dog)
- No CYP inhibition/induction identified from 6 different isoforms
- Protein binding, various species including rat and dog
- Blood-to-plasma ratio and plasma stability (several species)
- PK PO in Mouse, Gerbil, Rat and Dog
- PK IV in Rat and Dog

Regarding analytical methods, a fit-for-purpose bioanalytical (BA) method (LC-MS/MS) was developed for rat, dog, gerbil, and mouse plasma. Also, an analytical control method was developed for the determination of CC6166 in in vivo formulation.

The following properties of CC6166 are important and are to be considered for developing a suitable proposal.

- Oral administration
- Poor solubility profile
- Preclinical formulation is a spray drying dispersion (SDD)
### 4.2 Activities

<table>
<thead>
<tr>
<th>Activities</th>
<th>Title</th>
<th>Species</th>
<th>Description/notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bioanalytical Method development and validation</td>
<td>Rat plasma</td>
<td>To validate a method for CC6166 quantification in rat plasma that will be used during GLP studies GLP.</td>
</tr>
<tr>
<td>2</td>
<td>Bioanalytical Method development and validation</td>
<td>Dog plasma</td>
<td>To validate a method for CC6166 quantification in dog plasma that will be used during GLP studies GLP.</td>
</tr>
<tr>
<td>3</td>
<td>Dose formulation Method development and validation</td>
<td></td>
<td>To validate a method for the formulation that will be used during GLP rat and dog studies, and <em>in vitro</em> genotoxicity studies. GLP.</td>
</tr>
<tr>
<td>5</td>
<td>14-day oral tox study with a 14 day recovery period Including Irwin test With toxicokinetics, drug formulation analysis and bioanalysis</td>
<td>Rat</td>
<td>GLP</td>
</tr>
<tr>
<td>6</td>
<td>14-day oral tox study with a 14 day recovery period With toxicokinetics, drug formulation analysis and bioanalysis</td>
<td>Dog</td>
<td>GLP</td>
</tr>
<tr>
<td>7</td>
<td>Ames</td>
<td><em>In vitro</em></td>
<td>GLP</td>
</tr>
<tr>
<td>8</td>
<td>Chromosomal aberration</td>
<td><em>In vitro</em></td>
<td>GLP</td>
</tr>
<tr>
<td>9</td>
<td><em>In vivo</em> micronucleus study</td>
<td>Rat</td>
<td>Option 1: as a separate study Option 2: included in the 14-day rat tox study GLP.</td>
</tr>
<tr>
<td>10</td>
<td>hERG, HEK293 cells, physiological temperature</td>
<td><em>In vitro</em></td>
<td>GLP</td>
</tr>
<tr>
<td>11</td>
<td>CV Telemetry study with toxicokinetics, drug formulation analysis and bioanalysis</td>
<td>Dog</td>
<td>GLP</td>
</tr>
<tr>
<td>12</td>
<td>Respiratory study With formulation analysis</td>
<td>Rat</td>
<td>GLP</td>
</tr>
<tr>
<td>13</td>
<td>Drafting of nonclinical summaries for regulatory submissions</td>
<td>na</td>
<td>e.g. CTA, NDA under CTD format</td>
</tr>
<tr>
<td>14</td>
<td>Embryofetal development study dose range finding</td>
<td>Rat</td>
<td>Non-GLP</td>
</tr>
<tr>
<td>15</td>
<td>Embryofetal development definitive study</td>
<td>Rat</td>
<td>GLP</td>
</tr>
<tr>
<td></td>
<td>Bioanalytical Method development and validation</td>
<td>Rabbit plasma</td>
<td>To validate a method for CC6166 quantification in rabbit plasma that will be used during GLP studies GLP.</td>
</tr>
<tr>
<td></td>
<td>Study Type</td>
<td>Species</td>
<td>Study Type</td>
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<tr>
<td>16</td>
<td>Embryofetal development study dose range finding</td>
<td>Rabbit</td>
<td>Non-GLP</td>
</tr>
<tr>
<td>17</td>
<td>Embryofetal development definitive study</td>
<td>Rabbit</td>
<td>GLP</td>
</tr>
</tbody>
</table>
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 fitting with our requirements
  - Project management capabilities
  - Ability to conduct all activities (avoiding as much as possible outsourcing of activities)
  - Past experience with similar work

- **Financial criteria**
  - Realistic costing of the proposal in Euros

- **Ownership**
  - The contracting CRO must be >50% Japanese owned to fit within the project funding requirements (Japan GHIT).

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.
- Cost breakdown per activity and per sub-activities
- Outlines of protocols to be used
- Timelines per activity for the whole project (level of details per activities, cf 4.2)
- Feedback on DNDi Master Service Agreement Preclinical template (Annex 4): a bullet point list of issues has to be provided that your company would consider as being major concerns and imperatively require negotiation- together with a brief explanation
- Any other relevant information
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 experiment
- Final reports

6.3 Timelines

- Beginning of services planned for August 2021
- Internal Clinical candidate meeting and Clinical Trial Application are planned for July 2022

6.4 Additional information

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

7.ANNEXES

Annex 1: Intent to Participate letter

Annex 2: Q&A Form

Annex 3: Budget template