Request for Proposal

Class D Oligonucleotide CpG ODN D35

IND-enabling preclinical package

Dated: October 20, 2015
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1. PURPOSE

DNDi and its collaboration partners plan to develop a class D CpG oligonucleotide “D35” as an adjunct to chemotherapy for Cutaneous Leishmaniasis (CL) and Post Kala-Azar Dermal Leishmaniasis (PKDL). It is designed to activate the innate immune system and enhance the effector mechanism to control Leishmania infection.

The aim of this project is to demonstrate the suitability of CpG D35 for progression to phase 1 clinical trials. The objective for this proposal is to complete IND-enabling preclinical safety package as outlined below:

- In vitro and in vivo pharmacology studies to determine comparability between the immune response elicited by the GMP-grade CpG D35 is similar to the one used in all previous non-clinical studies. In vitro studies to compare responses for rats, monkeys (rhesus and cynomolgus) and humans.
- Pharmacokinetic studies including among others PK characteristics, in-vitro serum stability, in vitro hepatocyte clearance/metabolites profiling, development of bioanalytical (for toxicokinetics) and antidrug antibodies assays.
- Genotoxicity studies, including AMES screening test and in vitro micronucleus test
- Safety pharmacology, including hERG assay and inclusion of cardiovascular, respiratory and CNS endpoints in GLP toxicity studies
- Repeat dose toxicity studies, including dose ranging finding + GLP toxicological studies in two species (rodents and non-rodents). Readouts will include clinical signs, body weight, food consumption, haematology and blood chemistry, urinalysis, organ weights, histopathology, toxicokinetics and anti-drug antibodies.
- Reprotoxicology, including embryofetal development study in one or two species (e.g. rat and rabbit, although justification for rat only may be possible depending on assessment of relevance of rat as a species and whether it is used for general toxicity studies.

These studies are designed to estimate (1) Initial safe dose and subsequent dose escalation schemes in humans defined; (2) Potential target organs for toxicity identified and such toxicity is reversible (3) Safety parameters for clinical monitoring are determined

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 Class D Oligonucleotide CpG ODN D35 - IND-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 timelines, 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>20 October 2015</td>
</tr>
<tr>
<td>Send back the Intent to Participate letter</td>
<td>Service Provider</td>
<td>27 October 2015</td>
</tr>
<tr>
<td>Reception of proposals</td>
<td>DNDi</td>
<td>6 November 2015</td>
</tr>
<tr>
<td>Bidder selection</td>
<td>DNDi</td>
<td>16 November 2015</td>
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<tr>
<td>Contract signature</td>
<td>DNDi/Service Provider</td>
<td>18 December 2015</td>
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<tr>
<td>Project Start</td>
<td>Service Provider</td>
<td>Q1 2016</td>
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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. 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).

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>Questions types</th>
<th>Contact person</th>
<th>Title</th>
<th>Contact information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contractual &amp; technical aspects</td>
<td>Christophine Marty-Moreau</td>
<td>Procurement Manager</td>
<td><a href="mailto:cmarty@dndi.org">cmarty@dndi.org</a></td>
</tr>
</tbody>
</table>

2.3.3 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
  o Detailed proposal explaining how your company’s approach will enable DNDi team to meet project timelines and ensure quality results.

• A financial proposal
  o Budget template, attached as Annex 3 to be completed

2.3.4 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 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 diseases to address unmet needs that others are unable or unwilling to address.

The primary objective of DNDi 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, 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

CpG D35 is a D-type CpG ODN TLR9 agonist optimized for use in man. It stimulates maturation and activation of plasmacytoid dendritic cells, and production of pro-inflammatory cytokines such as interferon-γ (IFN-γ) and IL-12, which are required for control of the Leishmania infection, but has little or no effect on B cells, thereby minimizing the undesired TH2 type response associated with most other CpGs tested for other conditions. In addition, CpG D35 has demonstrated excellent in vivo efficacy against CL parasites in preclinical studies in both rodents and primates.

Although there is much positive experience with synthetic CpG ODNs in clinical trials, this particular CpG ODN sequence has not been tested in humans. However there are scientific justifications for omitting certain aspects of a standard preclinical program of studies: the (1) Absorption, distribution, metabolism, and excretion (ADME) behaviour of CpG ODN molecules is well understood and described in the literature. (2) ADME is driven by polyanionic chemical characteristics and often similar between sequences of a given chemistry. (3) Metabolite patterns are similar across species and urinary excretion of shortened oligonucleotides is the excretion route. (4) Clearance is via nuclease dependent mechanisms rather than P450-dependent. (5) Pharmacokinetics of ODNs scales well across species when bodyweight, rather than surface area, is used. (6.) Drug-drug interactions due to displacement of lipophilic drugs from plasma proteins or competition for P450 metabolism has not been reported for CpG ODN drugs similar to D35. (7) Anti-ODN antibodies have not generally been observed in preclinical studies.

For other aspects of preclinical safety, experience shows that CpG ODN molecules are not genotoxic, nor cardiotoxic. However, due to regulatory expectations in vitro genotoxicity and hERG studies are proposed in this package. The relevance of rodents for predicting human safety is questionable but most ODN products have used both rodents and non-human primates for GLP toxicity studies. All in vivo animal efficacy studies have used rhesus monkey rather than the cynomolgus monkeys which is the more standard NHP species for toxicity testing.

Currently 10g of API is available and an additional manufacture of 50g is planned for a delivery by Mid-January 2016.

4.2 Activities

4.2.1 Pharmacokinetics

- Development and validation of bioanalytical assay methods (e.g. LCMS) for the corresponding animal species (rat, Rhesus/cyno and human serum)
- ADA assay development
- In-vitro serum stability (rat, cyno, human)
- SC PK in Rhesus/Cyno and rat – conduct as part of DRF and GLP tox studies
- Serum sample analysis for the DRF and GLP tox studies
4.2.2 Genotoxicity studies

- AMES Screen test
- In-vitro micronucleus test (optional)

4.2.3 Safety pharmacology (optional)

- hERG assay

4.2.4 Toxicity study (DRF)

What is the body weight range for a Cyno and Rhesus in CRO facility? Is it possible to get small rhesus easily?

- Species: Cyno (or Rhesus) / Rats
- Administration: Subcutaneous
- No. of dose groups: 1 dose group for each of 1) single ascending dose and 2) repeated dose phase + 1 control group with repeat dosing of vehicle
- No. of animals/group: 1F, 1M for monkey and 5M, 5F for rats
- Dosing regimen: 1) Ascending single dose, nested design (10, 25 and 50 mg/kg,) each dose separated each by one week (D1, D7, D14) or two weeks (D1, D15, D29) washout period with necropsies 48h post dose. 2) Repeated dose phase, MTD (e.g. 50 mg/kg/week) given weekly or every 2 weeks for 3 doses.
- Sample collection for characterization of pharmacokinetic behaviour

4.2.5 Toxicity study (Repeated dose, GLP)

- GLP Compliant
- Species: Cyno (or Rhesus) / Rats
- Administration: Repeated administrations, subcutaneous
- Treatment Schedule 1: 5 doses: days 0, 7, 14, 21, 28
  OR, ALTERNATIVELY
- Treatment Schedule 2: 4 doses: days 0, 14, 28, 42
- Recovery period: duration of recovery period to be discussed (optional)
- No. of dose groups: 3 (or possibly 2) dose groups, plus 1 control group
- No. of animals total (CpG): 3M, 3F/dose group (monkey) 10M, 10F/dose group (rat)
- No. of animals total (recovery): 2M, 2F/dose group (monkey) (vehicle + high dose) M, 5F/dose group (rat) (vehicle + high dose)
- Sample collection for toxicokinetics
- Parameters:
  o Standard tox endpoints + safety pharmacology
o Body weight, clinical signs, ophthalmology, safety pharmacology (ECG, Blood pressure, respiratory rate, CNS observations)
o Clinical pathology: urine analysis, haematology, clinical chemistry, clotting parameters
o Organs weights, macro- and microscopic examination of full tissue list
o Cytokine analysis (D1, D15, D29, D43)
o CRP (C-reactive proteins) + complement factors C5a, C3a, Bb
o Immunophenotyping for lymphocyte subsets (+ ELISPOT?)
o ADAs for immunogenicity

4.2.6 Reprotoxicology (GLP Study)

- Rat embryofetal development study
- Rabbit embryofetal development study

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**
  o Project approach, methodology and planning
  o Experiences/skills, level of company representatives assigned to this project
  o Quality and applicability of proposal presentation
  o Customer references / Experience in related therapeutic area and country

- **Capacity to deliver**
  o Reasonable timelines
  o Project management capabilities
  o Ability to conduct all the services
  o Past experience with similar work

- **Financial criteria**
  Realistic costing of the proposal in Euros
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 for activity 3
- Outlines of protocols to be used
- Amount of test item needed for activity 1 and 2
- Timelines for the whole project
- Feedback on DNDi Technical Service Agreement template
- 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 beginning Q2 2016
- For analytical methods transfer and protocols, DNDi will be able to ship some of the 50g batch of CpG ODN D35 (ready by Mid-January) to initiate the work if needed.

6.4 Additional information
- DNDi will provide in due course 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: Budget template
Annex 4: Master Services Agreement Preclinical template