DNDi
Drugs for Neglected Diseases *initiative*

# Request for Proposal

# Pharmaceutical Development (Drug Substance & Drug Product) of CC6166 Targeting Onchocerciasis

Dated: June 21, 2021

# Table of Contents

# 1. PURPOSE

CC6166 compound from the treatment of Onchocerciasis 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.Onchocerciasis

Onchocerciasis, commonly known as river blindness, is a filarial disease caused by the parasitic nematode worm *Onchocerca volvulus*. People are infected by worms transmitted by the bite of blood-sucking blackflies, which breed in fast-flowing rivers.

River blindness is not usually fatal, but it inflicts hardship and misery on millions of people. In the human body, the adult worms produce embryonic larvae (microfilariae) that migrate to the skin, eyes and other organs. The worms can cause severe itching, disfiguring skin conditions, and blindness or impaired vision.

Efforts to eliminate river blindness are hampered in some areas by another parasitic infection known as Loiasis, or 'African eye worm'. Individuals with a very high amount of *Loa loa* larvae (microfilariae) in the blood are at risk of life-threatening complications if they receive ivermectin, a drug for river blindness.

## 1.2. Lead compound history

Rather than screen large representative libraries, DNDi has negotiated access to smaller focused chemical series with a greater probability of yielding drug candidates. These include:

- Indication sets (compounds which have progressed to clinical research but failed to reach the market because of reasons other than safety)
- Chemical series from other anti-infective research programs
- Chemical series from veterinary anti-infective research programs

Libraries of compounds have been screened through phenotypic assays against Onchocerca species (including *O. volvulus* the parasite causing onchocerciasis) to build a research portfolio focused on the development of drugs targeting the adult stage of the parasite. Through research sponsored by DNDi characterization of compounds occurred in several sites (UKB University of Bonn, The Griffin Institute – NPIMR, Museum of Natural History of Paris, New York Blood Bank Center).

In rare instances, compounds identified through screening of these libraries satisfied the criteria specified in DNDi's target candidate profile, but this expectation entails a considerable degree of luck because the compounds are not optimized as drug candidates for onchocerciasis. Nonetheless, hits against parasite targets that are derived from external drug discovery programs can still be considered as significantly lower risk candidates for lead optimization because considerable knowledge of structure-activity-relationships is available. This enables informed decision-making at an early stage both with regards to inclusion into a lead optimization program and progression through such a program.

Thus, excited about the screening results, Celgene decided to provide medicinal chemistry resources to support a discovery effort in collaboration with DNDi. As a result of this effort and following nomination of as a drug candidate, the next step for this molecule is to conduct a full GLP safety evaluation and pharmaceutical development to enable a First in Human study.

# 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* | 21 June 2021 |
| Send back the Intent to Participate letter | Service Provider | 30 June 2021 |
| Full Technical Package disclosed to participants | DND*i* | 02 July 2021 |
| Questions sent to DND*i* | Service Provider | 16 July 2021 |
| DND*i* responses to questions | DND*i* | 30 July 2021 |
| Reception of proposals | Service Provider | 13 August 2021 |
| Bidder Pre-selection notification | DND*i* | 27 August 2021 |
| Bid defense meetings | DND*i* | 06 September 2021 |
| Project award | DND*i* | 17 September 2021 |
| Project Start | Service Provider | 04 October 2021 |

## 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<br>Email: cmarty@dndi.org |
| Technical (until 30 July 2021) | Beatrice Bonnet | Senior Pharmaceutical Development Manager | Email: bbonnet@dndi.org |
| Technical | Anthony Simon | Pharmaceutical Development Manager | Email: asimon@dndi.org |

## 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 (10 steps synthesis) followed by cGMP manufacture of ~5 kg. Prior to the GMP manufacture, a demo batch on approx. 5 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-1_1) 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, API Methods development and validation (for assay&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

- 10 steps synthesis already performed up to 100 g from commercial available starting materials. The compound CC6166 has no chiral center
- Heavy metal removal
- 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 crystallisation development |
| 1.4 | Process safety assessment |
| 1.5 | Genotox Risk Assessment (GRA) of manufacturing process: ID all potential genotoxins in API |
| 1.6 | Polymorph screens (optional) |
| **Work Package 2 (Demonstration batch)** | |
| 2.1 | Purchase of raw materials/reagents to support demonstration batch manufacture (non-GMP) |
| 2.2 | Production of 5 Kg Demonstration Batch (non-GMP) with CoA and manufacturing report |
| **Work Package 3 (Analytical methods development and validation)** | |
| 3.1 | API Methods development and qualification (for assay&purity, residual solvent and cleaning) to comply with the Phase I regulatory Requirements (EU)<br>Analytical methods development and validation |
| 3.2 | Forced degradation studies for API HPLC method and report |
| 3.3 | Preparation and qualification of reference standards for RSM (Regulatory Starting Material), intermediates and final API with CoA |
| 3.4 | Preparation and qualification of analytical markers (impurity samples for RSM, intermediates and final API) with CoA |
| **Work Package 4 (GMP API manufacture)** | |
| 4.1 | Purchase of raw materials/reagents to support cGMP API manufacture |
| 4.2 | Production of 5 kg cGMP API with CoA, BSE/TSE |
| 4.3 | QC release testing including GMP Certificate of Analysis, QP release and campaign report |
| **Work Package 5 (Stability studies)** | |

| | |
|---|---|
| 5.1 | Stability program (long term storage 25°C/60%RH, intermediate storage 30°C/75%RH, and accelerated storage 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 (3-5g) 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:

- Micronisation and nanomilling with/without surfactant (to investigate the increasing of wettable surface area, size reduction without affecting the solid state (crystalline))
- Amorphous API (hot melt extrusion, spray drying)

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

Further refinement of the formulation used for GLP 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 (Formulation screening)** | |
| 1.1 | Formulation screening and final report |
| 1.2 | Prototype stability studies (5-6 formula) |
| 1.3 | Short term stability study (up to 4 formula) |
| 1.4 | Relative Bioavailability study in relevant animal model (dog or rat) - non GLP study: Optional |
| **Work Package 2 (Manufacture of Formulation for IND-Enabling Toxicology Studies)** | |
| 2.1 | Formulation for non-GLP toxicology studies and final report |
| 2.2 | In-use stability study (on extemporaneous formulation) as well as 6 months stability study at 25°C/60% RH (powder form) |
| 2.3 | Formulation for GLP safety/toxicology package |

| | |
|---|---|
| **Work Package 3 (Process Development of an oral dosage form for Phase I)** | |
| 3.1 | Formulation refinement |
| 3.2 | Development/Stability batch (~1-2kg) may be carried out on equipment intended for manufacture of Clinical batches<br>Batches size will be as follows:<br>Up to 2 capsule formulations: 1 active up to 3 dose strengths – 1 matching placebo<br>• Up to 3 dose strengths - Theoretical batch size ~2000/3000 capsules<br>• One matching placebo – Theoretical batch size ~2000/3000 capsules |
| 3.3 | 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 4 (Analytical method development and validation)** | |
| 4.1 | Assay and Related Substances Method (Accuracy, linearity and system precision, Method repeatability, Limits of detection and quantification (LOD and LOQ), Specificity and Solution stability) |
| 4.2 | Dissolution Method (Accuracy, linearity, system precision, specificity and filter compatibility, Solution stability and Method repeatability) |
| **Work Package 5 (Clinical batches manufacture for Phase I)** | |
| 5.1 | Manufacturing of clinical batch (capsules, 3 dose strengths, max 3000 units each) + matching placebo, max 9000 units |
| 5.2 | Packaging (bottles) for Phase I<br>Labelling for the clinical trials (2 languages) |
| 5.3 | QP release for the clinical use |
| 5.4 | Shipment to the single clinical site (in Europe) |
| **Work Package 6 (Stability studies on clinical batches)** | |
| 6.1 | Formal stability studies on up to two clinical batches: Active (three dose strengths) and matching placebo. Study duration five years (last two years optional), four storage conditions (25°C/60%RH optional, 30°C/75%RH, 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 between Mid-September to early October 2021
- Timelines for each activity subset should be clearly defined
- Completion of the service (including one month ICH stability data on the capsule clinical batches) in September 2023 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)
- Early pharmaceutical development overview (Drug Substance and Drug Product)
- Full details of work packages and deliverables
- Drug Product Manufacturing (IMP) and Packaging Quality questionnaires
- API quality questionnaire
- Pharmaceutical Development Services Agreement template

# 7. ANNEXES

Annex 1: Intent to Participate letter

Annex 2: Q & A Form