DNDi
Drugs for Neglected Diseases *initiative*

Request for Proposal

Pharmaceutical Development (Drug Product) of COVID Moonshot candidate(s)

Dated: September 29, 2021

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1. PURPOSE

COVID Moonshot is a highly accelerated discovery project aiming to identify an orally available treatment for COVID-19, with the current aim of being Phase I ready by 3Q2022. In order to perform all preclinical activities required to enable Phase I studies, DNDi is now sourcing a Contract Development and Manufacturing Organization (CDMO) offering pharmaceutical development capabilities to provide preclinical formulation support as well as drug product production and batch release ready for phase I activities.

1.1. COVID-19

The COVID-19 pandemic requires little introduction. Despite major efforts and breakthroughs in both vaccine development and deployment as well as therapeutic drug repurposing, at time of writing it remains clear that there is a significant need for SARS-CoV2-specific anti-viral therapeutics to control the pandemic.

A variety of high profile accelerated campaigns seeking novel anti-viral therapeutics are moving quickly through the clinic, most notably those from Pfizer (PF-07321332) which are currently completing Phase I studies. To maximize the chance of successful delivery of an orally available anti-viral treatment to patients, and to ensure global equitable access to all, DNDi have forged a partnership with the open-science Covid Moonshot project to enable rapid acceleration of a SARS-CoV2 main protease (MPro) inhibitor candidate towards the clinic. This work receives significant financial support from the Wellcome Trust, acting on behalf of the ACT-A initiative.

1.2. Lead compound history

The COVID Moonshot project originates with a high throughput crystallography fragment screen against the Main Protease, run at the Diamond Light source in March 2020. A highly effective crowdsourcing initiative was enabled to project to move towards low molecular weight, non-peptidomimetic and non-covalent inhibitors of the main protease, with the best compound demonstrating in vitro anti-SARS-CoV2 efficacy in the low nM range.

This work was achieved almost exclusively through an open science network engaging in-kind contributions from individuals, academics, experience pharmaceutical R&D consultant as well as biotech SMEs and pharmaceutical companies. Work has been performed in many labs worldwide, with the majority of the medicinal synthetic chemistry run at Enamine (Kiev, Ukraine). Pharmacology support comes from various sources including Weizmann Institute of Science, University of Oxford, Memorial Sloan Kettering Cancer Centre and Mount Sinai University Hospital, among others.

The accelerated nature of this project requires many of the classical drug discovery processes and paradigms to be run early on and “at risk”. The funding of this project, from Wellcome Trust, is focused on speed of delivery. As such, the project aims to identify (up to) five optimized lead compounds (OpLeads) and progress these through a well-defined preclinical cascade in parallel. Note that these five compounds will all come from the same

chemical series and therefore share significant structural similarity and possibly overlapping synthetic routes.

These five compounds will be triaged down to two Preclinical Candidate compounds (PreCC) at the exploratory / DFR toxicology stage, and then down to a single clinical candidate (CC) following the DRF toxicology evaluation, for progression through GLP toxicology and pharmaceutical development targeting a "Phase 1 ready" status for this final candidate compound, including submission of a Clinical Trial Application (CTA) dossier with the relevant health authority identified for the eventual Phase I studies. This will include having all material in hand ready for First in Human study.

The accelerated nature of the project therefore requires a pharmaceutical development package running "at risk" in parallel, with pharmaceutical development and formulation work focused initially on all five optimized leads, building in the flexibility to triage down to the selected candidate molecules as the preclinical data is generated, aiming to deliver drug product for Phase I on a single clinical candidate by project end. An overview of this process is seen in Fig 1.

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	DNDi	Sept 29th 2021
Q&A sent to DNDi	Service Provider	Oct 11th 2021
DNDi responses to Q&A	DNDi	Oct 15th 2021
Reception of proposals	DNDi	Oct 22nd 2021
Bid Defence Meetings (if any)	DNDi	4th week of October 2021
Bidder selection	DNDi	Nov 1st 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 DNDi 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 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 Bruno Discini (contacts details below).

Questions types	Contact person	Title	Contact information
Contractual	Bruno Discini	Senior Procurement Manager	Email: bdiscini@dndi.org
Technical	Anthony Simon	Pharmaceutical Development Manager	Email: asimon@dndi.org

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 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 and by molecule should be respected for DS and DP Services.
  - Payment Terms and payment schedule should be detailed in the quotation.

- Quality Questionnaires completed (templates will be provided as part of the technical package).

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 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, 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.
- Since the start of the COVID-19 pandemic DNDi has engaged a rapid response, coordinating a major clinical trial initiative in Africa (ATICOV) as well as engaging in major repurposing and novel anti-viral discovery approaches.

For more information, please visit DND*i* website: http://www.dndi.org/

4. SCOPE OF WORK

4.1. Drug Product

This document is a Request for Proposal for an estimate related to pharmaceutical development and drug product production on up to 5 compounds originating from the DNDI COVID moonshot project, as outlined in the figure below:

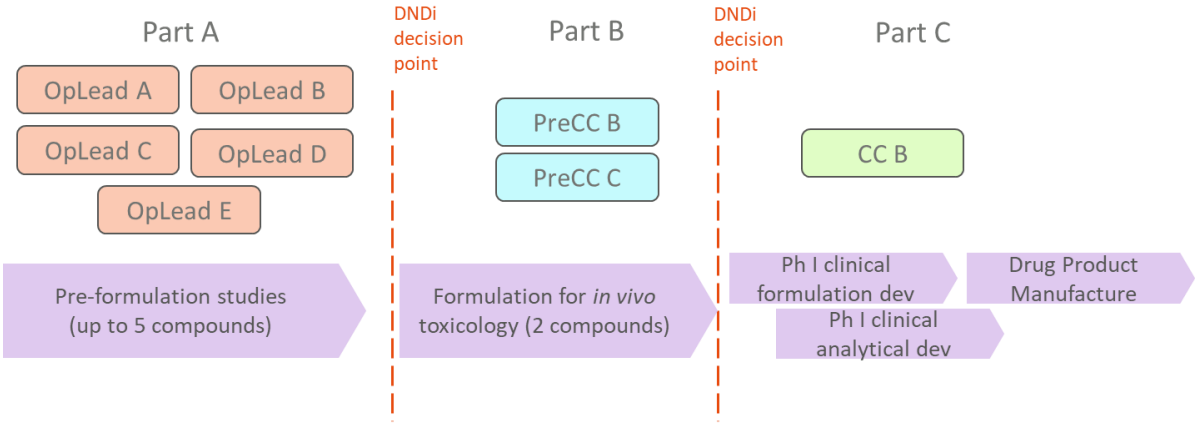

Fig 1; Representative overview of the proposal, starting from 5 optimized leads followed by prioritization down to two preclinical candidates PreCC, followed by prioritization of a single clinical candidate CC. Note the triggers for the DNDi decision points are decoupled from the progress made during pharmaceutical development process, and are instead informed by preclinical evaluation of the compounds performed in parallel and separate to this proposal, In this representative example compounds B and C are selected for part B, and compound B eventually prioritized for clinical candidate

Work packages relating to each of the stages within this proposal are outlined below:

- Work packages assume API has medium to high solubility in physiological pH range (≥ 0.5 mg/mL). Optional work packages are included to develop formulations for low solubility APIs as needed.
- Drug product batch sizes are indicative, final quantities will depend on drug loading, equipment size and clinical needs.

Please provide a price per compound for each work package.

WORK PACKAGE 1: PREFORMULATION STUDIES (UP TO 5 COMPOUNDS)

Assumption:

- Suitable solid form has been already identified (free base/acid, salt, polymorph).

Work:

pH solubility profile (pH 1.2, 4.5, 6.8)

Solubility profile with standard pharmaceutical co-solvents

Compatibility studies with standard pharmaceutical excipients

Optional activities:

- Solubility profiling in biorelevant media (FaSSGF, FaSSIF, FeSSIF).
- Extended screening with standard co-solvents and surfactants used for toxicology studies.
- Extended screening with excipients used for amorphous solid dosage forms.
- Evaluation of particle size reduction on dissolution rate.

Output:

- Preformulation report
- Formulation technology recommendation/selection

WORK PACKAGE 2: *IN VIVO* TOXICOLOGY FORMULATION (UP TO 2 COMPOUNDS)

Assumptions:

- Same formulation technology for all *in vivo* studies.
- Sufficient exposure in exploratory and DRF tox studies.

Work:

Development of suitable formulation for oral gavage in rat and dog (simple solution or suspension preferred), to be prepared extemporaneously by toxicology CRO.

Verification of dose formulation preparation and in-use stability (up to 7 days).

Optional:

- Formulation manufacture for GLP studies (e.g. intermediate product for supply to toxicology CRO).

Outputs:

- Tox formulation development report.
- Dose formulation preparation procedure.

WORK PACKAGE 3: PHASE 1 CLINICAL FORMULATION DEVELOPMENT (1 COMPOUND)

Assumptions:

- First intent is to develop a simple, flexible oral formulation that can be prepared extemporaneously.
- Two strengths for bottles, capsules or tablets.

Work:

Prototype formulation development:

- API in bottle for oral solution or suspension (plus vehicle).
- API in capsule (manual or semi-automated fill).
- Simple powder blend in capsule (one lead formulation and one back-up).
- Conventional immediate release tablet (one lead formulation and one back-up).
- Short-term stability studies on prototype formulations (≤ 3 months) and clinical packaging recommendation, including accelerated and stress conditions.
- Formulation selection for Phase 1 clinical trials (after 1 month stability).
- Development of visually-matched placebo.

Process development for selected formulation:

- Preparation instructions and in-use stability for extemporaneous formulations.
- Process development for non-extemporaneous formulations (capsule or tablet formulations).
- Non-GMP development batch manufacture – two strengths.
- Batch sizes:
  - API in bottle: 250 per unit strength
  - API in capsule: 250 per unit strength
  - Simple powder blend in capsule: 2500 per unit strength
  - Conventional tablet or capsule: 2500 per unit strength

Stability studies:

- Three-year stability study on development batches – two strengths in clinical packaging.

Optional :

- Formulation and process development for amorphous solid dosage forms, if needed.

Outputs:

- Formulation development report
- Process development report
- Interim and final stability summaries

WORK PACKAGE 4: DRUG PRODUCT ANALYTICAL DEVELOPMENT (1 COMPOUND)

Assumptions:

- Final specifications and methods will depend on the dosage form selected.

Work:

Development of stability-indicating of HPLC method for assay and related substances.

Development of dissolution method.

Method validation suitable for Phase 1 clinical trials.

Validation of microbiological tests.

Optional:

- Evaluation of additional characterisation tests for amorphous solid dosage forms

Outputs:

- Method development and validation reports.
- Finished product specifications (for manufactured dosage forms).

WORK PACKAGE 5: PHASE 1 CLINICAL MANUFACTURE (1 COMPOUND)

Assumptions:

- Not required for formulations prepared extemporaneously in the Phase 1 unit.

- Two strengths for bottles, capsules or tablets.

Work:

GMP manufacture of clinical batches (two strengths) and matching placebo in bulk:

- API in bottle: 750-1000 per unit strength
- API in capsule: 750-1000 per unit strength
- Simple powder blend in capsule: 5000-10000 per unit strength
- Conventional tablet or capsule: 5000-10000 per unit strength
- Placebo batch sizes: To match corresponding active

Primary packaging of clinical batches.

Clinical trial labelling.

QP certification.

Distribution to clinical site using qualified courier (with temperature loggers).

Optional:

- Manufacture of ready to use vehicle for reconstitution of API in bottle.

Outputs:

- Certificates of analysis.
- QP certificates of conformance.
- Executed batch manufacturing records.

WORK PACKAGE 6: STABILITY STUDIES (1 COMPOUND)

Assumptions:

- Not required for formulations prepared extemporaneously in the Phase 1 unit.

Five (5) year stability studies on clinical batches.

Five year stability study on placebo (with minimal testing e.g. appearance, disintegration, microbiological).

Outputs:

- Interim and final stability summaries

4.2. Overall timelines

Understanding that timelines may vary due to project complexity as well as delays resulting from activities outside the scope of this proposal, we are aiming for the following timelines:

Month 0: First OpLead structure disclosed to CDMO.

Months 1-2 Remaining four OP Lead structures disclosed.

Month 4 Triage from 5 x OpLeads to 2 x PreCC.

Month 7 Delivery of formulations for *in vivo* toxicology studies for 2 PreCC.

Month 12 Drug Product manufacture for Clinical Candidate.

Month 13 Batch release for Phase I material.

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 total cost of the offer.

Proposals will be assessed against the main following criteria but not limited to:

- **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.
  - The CDMO is able to work to the short timelines required for this accelerated COVID-19 response project with a high degree of flexibility.
  - 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.
- **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.
- **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 2.3.3.
- 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 Package per compound for DP Services. Include estimations as to how these costs may vary once presented with the actual compound structures. In addition, include precise cost structure for taking the "dummy" example compound through the entire process.
- Projected timeline, including any discrepancy or issue with the proposed timelines in 4.2.
- 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 (WP1) planned to start January 2022.
- 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 March 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 Product).
- Full details of work packages and deliverables.
- Quality questionnaire (will be provided as part of the tech package).
- Pharmaceutical Development Services Agreement template.

7. ANNEXES

Annex 1: Intent to Participate letter

Annex 2: Q & A Form