Request for Proposal

COVID Moonshot CTA-enabling Toxicology package

Dated: September 29th 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 Research Organization (CRO) offering an integrated platform capable of delivering the nonclinical safety and toxicology aspects of the project.

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 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.

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.

These five compounds will be triaged down to two Preclinical Candidate compounds (**PreCC**) at the exploratory / DRF toxicology stage, and then down to a single candidate

PreCC 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.

The accelerated nature of the project therefore requires a preclinical package running "at risk" in parallel. In particular this means we require five (5) compounds run in parallel through the non-clinical safety and DRF-preparation elements of the work package (DRF formulation development, bioanalysis), followed by progression of two of these compounds run in parallel through the exploratory / DRF toxicology in both species. An overview of this process is seen in Fig 1

The objective of this proposal is to complete CTA-enabling preclinical safety package taking into consideration the following points:

1. Work that has already been done (see Compound Information)
2. Compound profiling that will be done prior to initiating the studies in this package, but which will be communicated prior to the start of the work. – note that this may require proactive flexibility from the provider to add or alter elements of the nonclinical safety plan, and to communicate cost and timeline impact(s) to DNDi, depending on the nature of these yet-to-be communicated results (e.g. if additional preclinical toxicology studies are deemed necessary by these results.
3. Timelines for initiation of the non-clinical safety profiling studies in this RFP is end of Q12022:
   - Preliminary activities:
     - Bioanalysis development to start early April 2022 at the latest (5 OpLead compounds).
     - PK assessment of nonclinical oral formulation in rat and dog* to start May-June 2022 at the latest (2 PreCC Compounds only).
   - DRF pilot toxicology in Rat to start July 2022 (2 PreCC Compounds)
   - DRF pilot toxicology in Dog* to start August 2022(2 PreCC Compounds)
   - Ultimate study on the critical path: 14-day toxicity study in both rat and dog* (1 PreCC compound).
   - Completion of preclinical package (audited draft reports, at minimum): January 2023.
   - Clinical candidate nomination for Phase 1: February 2023

4. Dog* as the non-rodent species.
5. An appropriate Project Management approach where all activities/studies will be performed, analyzed, and discussed in an integrated manner with the Sponsor and Sponsor's toxicology consultants.
6. DNDi and DNDi donors in general are requiring particular care to animal welfare and use the NC3RS as advisor body. For this purpose and if not done yet, we are encouraging all applicants to familiarize with the various guidelines and requirements by the NC3Rs website and take note of the recommendations we will follow for

selecting an appropriate contractor (see Annex 4).

7. Note: Clinical Phase I will be conducted in Europe.

** Dog is anticipated to be selected as the non-rodent species and the proposal must be elaborated in that sense. However, at this stage, the sponsor cannot exclude that this choice will not evolve (data-driven) and the vendor is asked to comment on the cost and timelines impact if a switch to either minipig or NHP became necessary.*

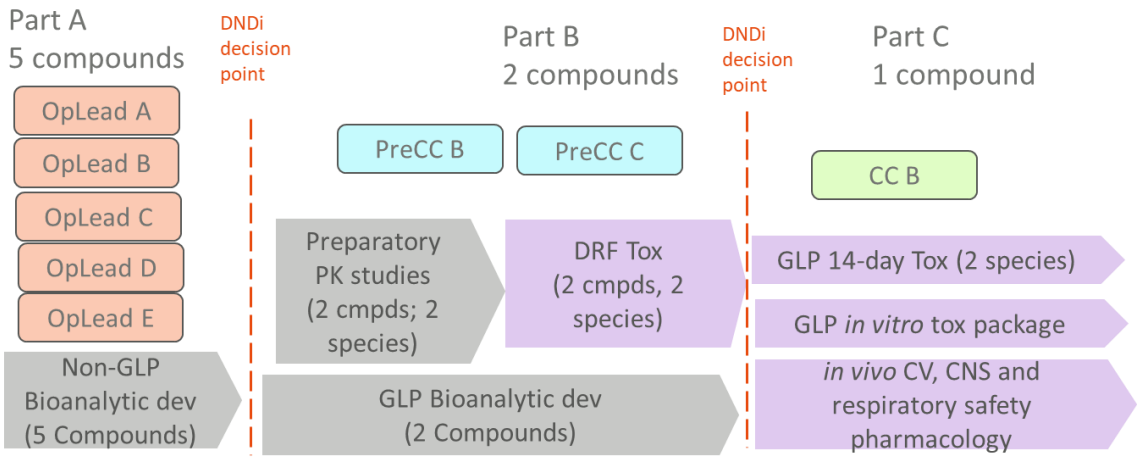

Fig 1: Flow chart for this work package following hypothetical scenario that of Five OpLeads A-E, first decision point triages to compounds B and C, and second decision points triages to compound B.

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 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 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	Stephanie Braillard	Nonclinical development Senior Manager	Email: sbraillard@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 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.

- 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:
  - Activities list, including outline study plans, an any study design considerations.
  - Timing (initiation phase, experimental phase, draft report for each activity), ideally with a draft Gantt chart.
  - Comment on the cost and timelines impact if a switch to either minipig or NHP became necessary.
  - Answers to the NC3Rs standard questions about the use of dogs (Annex 4).

- 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 provided.
  - Payment Terms and payment schedule should be detailed in the quotation.

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, 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.
- 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 DNDi website: http://dndi.org

4. SCOPE OF WORK

4.1. Compound information

Lead compounds from the COVID Moonshot project are small organic compounds demonstrating excellent *in vitro* efficacy against the main protease of SARS-CoV2 (MPro) as well as anti-viral efficacy in SARS-CoV2 infection assays. They display pharmacological and physico-chemical properties consistent with DNDi COVID-19 Target Product Profile and will be developed as an oral treatment of maximum 10-day dosing (targeted clinical dosing schedule of BID or TID oral dosing for 5 days)

The following data on the five OpLeads's will be communicated prior to initiation of the work in this proposal. *Note: compounds demonstrating major flags in any of the following will not be proposed as OpLead compounds for evaluation in this work.*

- Genotox profiling : mini-AMES, *in vitro* Micronucleus (non-GLP).
- hERG patch clamp, plus additional sodium and calcium channel profiling.
- Various Safety screen panels (transporter panel, Eurofins safety panel) and cytotoxicity measurements.
- Stability in liver microsomes and hepatocytes, various species including rat, dog, minipig, cynomolgus and human.
- Protein binding, various species including rat, dog, minipig, cynomolgus and human
- Blood-to-plasma ratio, Brain-lung-plasma ratio.
- Plasma stability (several species, including rat, dog, minipig, cynomolgus and human).
- PK PO in Rat and Dog (or other nonrodent species).
- PK IV in Rat and Dog (or other nonrodent species).
- CYP induction and inhibition, including TDI.
- Preliminary Human dose prediction estimation.
- Non-rodent species selection.

Preliminary formulation details and bioanalytical (BA) methods developed for PK studies will be communicated for each PreCC.

Based on evaluation of current front-runner compounds, the following characteristics of Moonshot compounds are important and are to be considered for developing a suitable proposal.

- Oral administration.
- Moderate solubility, good permeability, acceptable bioavailability.
- Compounds may be free base or may be in salt form (case-by-case basis).

4.2. Activities

Work Package ID	Title	Species	Number of compounds	Description/notes
1	Bioanalytical Method development and validation (non-GLP)	Rat and Dog*	5 (OpLeads)	Non-GLP. To validate a methods for (up to) five Moonshot Compound(s) with quantification in rat plasma that will be used during GLP studies.
2	PK studies	Rat and Dog*	2 (PreCC)	Goal is to check and validate the exposure following the administration of Moonshot Compound(s) with the new developed toxicology formulation. 3 three different dose levels . Fit-for-purpose analytical methods can be used for quantifying Moonshot Compound(s) in plasma and in formulation for use in DRF studies.
3	Bioanalytical Method development and validation (GLP)	Rat plasma	2 (PreCC)	GLP. To validate a method for Moonshot Compound(s) with quantification in rat plasma that will be used during GLP studies. Including long term stability (2 weeks, 1 month and 3 months).
4	Bioanalytical Method development and validation.	Dog* plasma	2 (PreCC)	GLP. To validate a method for Moonshot Compound(s) with quantification in dog plasma that will be used during GLP studies. Including long term stability (2 weeks, 1 month and 3 months).
5	Dose formulation Method development and validation (*in vivo*)	Rat and Dog*	2 (PreCC)	GLP. To develop and validate a method for the formulation that will be used during GLP rat and dog* studies. Including assessment of formulation stability.

6	Dose formulation Method(s) development and validation (*in vitro*)	*In vitro*	1 (CC)	To develop and validate a method for the formulation that will be used during *in vitro* GLP tests (genotoxicity and hERG). Including assessment of formulation stability.
7	MTD and 7-day DRF toxicity study.	Rat	2 (PreCC)	Non-GLP. MTD phase: 4 dose escalations, staggered, 3/sex/group, 3 day dosing Repeat dose phase (DRF): 3/sex at 3 dose levels + vehicle control Additional 3/sex/group for TK on days 1 and 7. Including bioanalysis and TK. Including histopathology on abbreviated list of tissues (liver, lung, heart, brain, spleen, eye). Including assessment of lung:plasma exposure ratio (at end of study) Including collection of plasma samples for potential metabolites identification.
8	MTD and 7-day DRF toxicity study	Dog*	2 (PreCC)	Non-GLP. MTD phase 1M/1F (dogs re-used in DRF phase), 4 dose escalations, 3-day dosing Including bioanalysis and TK limited on a couple of timepoints/dose/animal. Repeat dose phase 1M/1F at 3 dose levels, no control group. Including bioanalysis and TK. Including ECG with jackets on day 1. Including histopathology on abbreviated list of tissues (liver, lung, heart, brain, spleen, eye). Including collection of plasma samples for potential metabolites identification.
9	14-day repeat dose oral toxicity study with a 14- day recovery period.	Rat	1 (PreCC)	GLP. Including DFA, bioanalysis and TK.

10	14-day repeat dose oral toxicity study with a 14- day recovery period.	Dog*	1 (PreCC)	GLP. Including DFA, bioanalysis and TK.
11	Bacterial Mutation Assay (Ames assay)	*In vitro*	1 (PreCC)	GLP. Including dose formulation analysis. ± S9
12	Rat Micronucleus Test	Rat	1 (PreCC)	GLP Including dose formulation analysis and bioanalysis (requiring formulation allowing up to 2000 mg/kg)
13	*in vitro* micronucleus	*In vitro*	1 (PreCC)	GLP. Human peripheral blood lymphocytes. Including dose formulation analysis. ± S9
14	hERG,	*In vitro*	1 (PreCC)	GLP. HEK293 or CHO cells. Physiological temperature Including bath concentration analysis.
15	CV Telemetry study	Dog*	1 (PreCC)	GLP. Cross-over design. Including DFA. Optional: a few TK timepoints and bioanalysis.
16	Respiratory safety pharmacology	Rat	1 (PreCC)	Whole body plethysmography As part of the 28-day pivotal study or as stand-alone study.

17	CNS safety pharmacology	Rat	1 (PreCC)	Rat Irwin As part of the 28-day pivotal study or as stand-alone study.
18	Identification of circulating metabolites from plasma	Rat and Dog*	2 (PreCC)	Non-GLP. As an option.

* Dog is anticipated to be selected as the non-rodent species and the proposal must be elaborated in that sense. However, at this stage, the sponsor cannot exclude that this choice will not evolve (data-driven), and the vendor is asked to comment on the cost and timelines impact if a switch to either minipig or NHP became necessary.

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, 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**
  - Timelines fitting with our requirements, including capacity to run multiple molecules in parallel.
  - Project management capabilities.
  - Willingness to work together in a partnership mode.
  - Ability to conduct all activities (avoiding as much as possible outsourcing of activities).
  - Ability to conduct dog, NHP or minipig studies.
  - Past experience with similar work.
- **Ethical criteria**
  - Ability to comply with the principles of Wellcome Trust grant funding conditions regarding animal use: https://wellcome.org/grant-funding/guidance/use-animals-research-policy.
  - 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 2.3.3. regarding detailed proposals requirements. Please make sure that the reader can easily make the link between activity scope, timelines and cost.

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 experimental phase, 8 weeks when it concerns a GLP study.
- Final reports.
- Technical, scientific, and regulatory advice through the length of the project.

6.3 Timelines

- Beginning of services planned in Jan 2022.
- Availability of material for non-GLP bioanalysis work (activity 1): Jan 2022.
- Availability of API and SLIS for activities 2 to 18: April 2022.
- Completion of preclinical package (audited draft reports, at minimum): Jan 2023.

6.4 Additional information

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

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