DNDi
Best Science for the Most Neglected

Request for Proposal

Moonshot/ASAP Preformulation and Formulation Development

Dated: October 25, 2024

1. PURPOSE

To enable Phase I studies for ASAP-0017445, a broad-spectrum coronavirus inhibitor, DNDi is sourcing a Contract Development and Manufacturing Organization (CDMO) with pharmaceutical development capabilities. The CDMO will focus on preformulation initially, and later-on formulation development subject to downstream funding being secured, to ensure readiness for potential GMP drug product production and Phase I activities by 2027.

2. PROJECT OVERVIEW

The COVID Moonshot project is a global, open-science collaboration aiming to develop safe, affordable antiviral drugs for COVID-19 and future pandemics. Launched in March 2020, the initiative brought together over 150 scientists to identify molecules inhibiting SARS-CoV-2. DNDi was awarded a Wellcome Trust grant to enable late-stage lead optimisation and preclinical development of the Moonshot lead DNDI-6510. Development of DNDI-6510 was later discontinued due to significant metabolic clearance and PXR receptor activation in preclinical studies.

The follow-on NIH-funded discovery consortium ASAP (AI-driven Structure-enabled Antiviral Platform (ASAP) further optimized the COVID Moonshot series, and developed a novel, broad-spectrum coronavirus main protease (MPro) inhibitor. ASAP-0017445 is a broad-spectrum coronavirus antiviral inhibitor with excellent potency against human lethal coronaviruses SARS-CoV-2 and MERS-CoV, a promising PK profile, and good preliminary safety and toxicology profiling in vitro. Significant progress has been made in scaling up chemistry efforts, and the project is now advancing ASAP-0017445 to dose-range finding (DRF) toxicology studies in rats and dogs. Utilizing the remaining funds from the Wellcome Trust grant awarded to DNDi, ASAP-0017445 will now be advancing to early preclinical development.

2.1 Lead Compound History and Transition

The initial focus of the COVID Moonshot project was to develop an orally available treatment for COVID-19, specifically targeting SARS-CoV-2 main protease (MPro) inhibitors. The COVID Moonshot project originated from a high-throughput crystallography fragment screen conducted at Diamond Light Source in March 2020. Through a successful crowdsourcing initiative, the project quickly identified low molecular weight inhibitors of the SARS-CoV-2 MPro enzyme.

In parallel to scale-up and preclinical profiling of the COVID Moonshot lead compound DNDI-6510, the COVID Moonshot discovery team continued its work as the ASAP consortium, funded through the NIH funding scheme AViDD (Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern), shifting its focus towards broad-spectrum antiviral inhibitors against coronaviruses, enteroviruses and flaviviruses.

This effort led to the discovery of ASAP-0017445, a broad-spectrum coronavirus antiviral inhibitor with excellent potency against human lethal coronaviruses SARS-CoV-2 and MERS-CoV, a promising PK profile, and good preliminary safety and toxicology profiling *in vitro*. Significant progress has been made in scaling up chemistry efforts, and the project is now advancing ASAP-0017445 to dose-range finding (DRF) toxicology studies in rats and dogs. Utilizing the remaining funds from the Wellcome Trust grant awarded to DNDi, ASAP-0017445 will now be advancing to early preclinical development.

2.2 ASAP-0017445: The Current Focus

DNDi is seeking a CDMO to assist with two key work packages: **preformulation** and **formulation development.**

2.3 Timelines, Parallel Development, and Grant Funding

The preformulation work is scheduled to start in February 2025. The pharmaceutical development of ASAP-0017445 will proceed in parallel with preclinical in vitro and in vivo studies. DNDi aims to select a CDMO with the capability of delivering all three WPs. Preformulation work (Work Package (WP) 1 and 2) will contracted to the awarded provider and be funded through an existing Wellcome Trust award to DNDi.
DNDi is currently working on follow-on applications to various funders to secure additional funds for later-stage preclinical development, including the anticipated formulation studies (WP3). WP3 will be considered by DNDi to select the provider, but not contracted until additional funding is secured.

3. RFP INSTRUCTIONS

3.1 General information

- DNDi invites you as a Service Provider to submit one proposal covering all services described in Section 5.
- 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.
- All bidders are required to complete and return the Intent to Participate letter.
- The issuance of this 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.
- 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 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 DNDi will consider necessary

- Late submission proposals are subject to rejection.
- DNDi 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.
- All offers should be submitted in an electronic format.
- The proposed timelines below indicate the process DNDi intends to follow. If there are changes to this timeline, DNDi will notify you in writing.

3.2 Timelines

Process steps	**Responsible party**	**Timelines**
Launch RFP	DNDi	October 25th 2024
Confirmation of Intent	Provider	October 30th 2024
Technical package	DNDi	October 31st 2024
Questions sent to DNDi	Provider	November 5th 2024
DNDi responses to questions	DNDi	November 7th 2024
Submission of proposals	Provider	November 15th 2024
Bidders preselection notification	DNDi	November 22nd 2024
Bid defense meetings (if any)	DNDi & Provider	November 28th 2024
Due Diligence	DNDi	Week of Dec 2nd 2024
Project award notification	DNDi	December 9th 2024

3.3 RFP processes and contact information

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 3.2 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 3.2. Timelines of the RFP.

To submit your questions, please use the form attached as Annex 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 section 3.2.

Confirmation of intent should be sent by email to Christophine Marty-Moreau (contacts details below). A technical package (Annex 3) will be shared upon receipt of the Confirmation of intent.

Questions types	Contact person	Title	Contact information
Contractual	Christophine Marty-Moreau	Senior Procurement Manager	Email: cmarty@DNDi.org
Technical	Anthony Simon	Pharmaceutical Development Manager	Email: asimon@DNDi.org

3.4 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

- 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 DNDi to assess the opportunity of contracting with your company

- A technical proposal
  - Detailed proposal explaining how your company approach will enable DNDi team to meet project timelines, deliverables and ensure quality results.

- **A financial proposal**

Budget to be provided for all activities detailed in section 5, the cost breakdown by Work Packages

3.5 Conflict of Interest

The Company shall disclose any actual or potential conflicts of interest in the Intent to Participate letter.

4. 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 25 new treatments by 2028 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 in a rapid response, coordinating a major clinical trial initiative in Africa (ANTICOV) as well as engaging in major repurposing and novel anti-viral discovery approaches.

For more information, please visit DNDi website: http://www.DNDi.org/

5. SCOPE OF WORK

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

- Work packages assume API has low solubility in physiological pH range. 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.

WORK PACKAGE 1: PREFORMULATION STUDIES

Assumptions:

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

Work:

- pH solubility profile (pH 1.2, 4.5, 6.8)
- Solubility profiling in biorelevant media (FaSSGF, FaSSIF, FeSSIF)
- Solubility profile with standard pharmaceutical co-solvents
- Compatibility studies with standard pharmaceutical excipients

Optional activities:

- 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: DRUG PRODUCT ANALYTICAL DEVELOPMENT

Assumptions:

- Final specifications and methods will depend on the dosage form selected
- This work package should be included in the proposal, but work will be subject to DNDi securing follow-on funding for this project

Work:

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

Optional:

- Evaluation of additional characterization tests for amorphous solid dosage forms

Outputs:

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

WORK PACKAGE 3: PHASE 1 CLINICAL FORMULATION DEVELOPMENT

Assumptions:

- This work package should be included in the proposal, but work will be subject to DNDi securing follow-on funding for this project
- 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
- 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 activities:

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

Outputs:

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

6. 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:

6.1 Technical criteria

- The CDMO will have the capability and experience/expertise to perform all the activities in a licensed facility at the scale outlined in "Scope of Work".
- The CDMO is able to work to short timelines with a high degree of flexibility.
- DNDi is looking for a CDMO that has renowned credentials in running successful development projects for small organizations.

6.2 Capacity to deliver

- DNDi 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.

6.3 Financial criteria

- Realistic costing of the proposal with NGO rates whenever possible for the 3 Work Packages.

7. PROPOSAL REQUIREMENTS, DELIVERABLES & TIMELINES

7.1 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 3.4
- Complete scope of work description, with a full list of activities 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.

- Project team involved
- List of tasks and responsibilities
- Projected timelines
- Realistic project Gantt Chart detailing the project schedule from start to finish, including multiple options if appropriate.
- Any other relevant information

7.2 Terms and Timelines

- Beginning of Services (WP1 and WP2) planned to start February 2025
- Timelines for each activity subset should be clearly defined
- Work on WP3 will not be included in initial contracting, as subject to downstream funding being secured; therefore
    - Costing and timelines for WP3 should be included in the proposal
    - A tentative start date for WP3 is estimated as Q1 2026

7.3 Additional information

After receiving their Intent to Participate letter, DNDi will provide the bidders with the technical package with available information on the API.

8. ANNEXES

Annex 1: Intent to Participate letter
Annex 2: Q&A Form
Annex 3: Technical Package (to be provided at a later stage)