Request For Proposal

Clinical Trial Supply Services
for Phase 3 Trial in Uncomplicated Gonorrhea

Date: September 18th, 2018

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1. PURPOSE

GARDP is a not-for-profit research and development organization that addresses global public health needs by developing and delivering new or improved antibiotic treatments, while endeavouring to ensure sustainable access. Initiated and incubated through close collaboration between WHO and Drugs for Neglected Diseases initiative (DNDi), GARDP's mission is to work in partnership with the public and private sectors, to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists. GARDP is currently hosted and facilitated by DNDi, which provides the scientific environment, necessary personnel, and infrastructure to ensure an effective start-up phase.

For more information, please visit GARDP website: https://www.gardp.org/

GARDP plans to conduct a multi-centre, randomised, open-label, non-inferiority trial to evaluate the efficacy and safety of a single, oral dose of zoliflodacin compared to up to two comparators in the treatment of patients with uncomplicated gonorrhoea. GARDP is sourcing a CRO offering Clinical Trial Supply Services for this Phase 3 Trial in Uncomplicated Gonorrhoea.

2. REQUEST FOR PROPOSAL INSTRUCTIONS

2.1 General Information

a) GARDP invites you as a Service Provider to submit one proposal covering the 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 GARDP to make an award. GARDP is under no obligation to justify the reasons of its choice of service provider following the competitive bidding. GARDP may choose not to justify its business decision to the participants of the RFP.

e) GARDP 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 a proposal other than the one containing the lowest financial offer
- Award a contract on the basis of initial proposals received without discussion of best and final offers
- Award all services to only one supplier or allocate parts of them to different suppliers according to the needs of GARDP

f) Proposals submitted after the deadline are subject to rejection.

g) GARDP reserves the right to request additional data, information, discussions or presentations to support each 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) Service providers are responsible for ensuring the accuracy of information provided in support of their proposal. GARDP reserves the right to reject an awardee in the event of failure to disclose any material information, or material changes or errors in any information on which the award decision was based.

j) The proposed timelines below indicate the process GARDP intends to follow. If there are changes to these timelines, GARDP will notify you in writing.

2.2 Timelines

Process Steps	**Responsible Party**	**Timelines**
Launch Request For Proposal	GARDP	18 September 2018
Send Back the Intent to Participate Letter	Service Provider	25 September 2018
Confidential information disclosed to participants	GARDP	27 September 2018
Questions Directed to GARDP	Service Provider	4 October 2018
GARDP Responses to Questions	GARDP	12 October 2018
Receipt of Proposals	GARDP	26 October 2018
Notification to Pre-Selected Bidders	GARDP	12 November 2018
Bid Defence Meetings	GARDP and Service Providers	19-20 November 2018
Selection of Service Provider	GARDP	23 November 2018
Project Start	Service Provider	1 February 2019

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 GARDP 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 GARDP with a written confirmation of intent or decline to participate by the date as indicated in the section 2.2.
Please, note that the "Intent to participate letter" is a standard document which GARP cannot afford negotiating due to projects priorities, time and resources dedication. This template is based on several years of experience working with suppliers and contains widely acceptable terms in RFPs.

Confirmations of intent should be sent by email to Christophine Marty-Moreau (contacts details below).

Question Types	**Contact Person**	**Title**	**Contact Information**
Financial	Christophine Marty Moreau	Senior Procurement Manager	Phone:+41 22 906 92 61 Email: cmarty@dndi.org
Technical	Anthony Simon	Pharmaceutical Development Manager	Phone: +41 22 907 78 94 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 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 testimonials, pricing strategy for NGOs.
  - List of bullet points of high level comments on the attached GARDP Services Agreement template (points that are non-negotiable or very important for your company). This information will form some of the decision criteria for the award process.
  - Any other relevant information enabling GARDP to assess the opportunity of contracting with your company.

- A Technical Proposal
  Detailed proposal explaining how your company's approach will enable GARDP team to meet project timelines and ensure quality results.

- A Financial Proposal

2.5 Conflict of Interest

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

3. GARDP STI PROGRAM OVERVIEW AND PROJECT BACKGROUND

3.1 Program Overview

GARDP R&D strategy for Sexually Transmitted Infections aims at delivering, within 7 years-time, at least one treatment that i) works against drug-sensitive and drug-resistant gonorrhea; ii) is suitable for integration into WHO-recommended STIs case management (including syndromic management); iii) works in both uro-genital and extra-genital (i.e. pharyngeal and anorectal) infections. In order to fulfill this aim GARDP has partnered with Entasis Therapeutics to accelerate the development and registration of Zoliflodacin for the treatment of uncomplicated gonorrhea. It constitutes the first and main priority of the overall STI program.

The objective of the GARDP zoliflodacin project is to accelerate the development and registration of zoliflodacin, a first-in-class oral gyrase inhibitor that has shown high efficacy in adult patients with uncomplicated urogenital gonococcal (GC) infection.

3.2 Uncomplicated Gonorrhea

Gonorrhea is one of the most common Sexually Transmitted Infections (STIs), affecting 78 million people every year. The Western Pacific and African regions have the highest incidence, with 89 and 50 cases per 100'000 population respectively. In the USA it causes 400'000 infections per year and is the second most frequently reported notifiable infectious diseases. There are serious concerns, articulated by the WHO and others, over the spread of resistant gonorrhea. *Neisseria gonorrhoeae*, the causative agent of gonorrhea, has been included as one of three organisms presenting an urgent threat to public health by the US Center for Disease Control (US CDC) and is listed as a "high priority" pathogen in the WHO Global priority list of antibiotic-resistant pathogens.

Gonococcal infections commonly manifest in men as urethritis. Symptoms of urethritis develop in 75% of the men within four to eight days of genital infection with *N. gonorrhoeae* and in 80 to 90% within two weeks. Urethral discharge is the most frequent presenting symptom and is often undistinguishable from non-gonococcal urethritis (e.g. in *Chlamydia trachomatis* infections). In women, gonococcal infections are often (≥50% of the cases) asymptomatic. Genital infections, in particular cervical infections, are the most common infections. When symptomatic, cervical infection typically manifests as vaginal discharge. If left untreated, *N. gonorrhoeae* infections can ascend to involve the uterus and fallopian tubes, with dramatic consequences on reproductive health. Pelvic inflammatory disease (PID) occurs in 10-20% of women with cervical gonorrhea and *N. gonorrhoeae* is thought to be a leading cause of PID worldwide.

Single dose antimicrobial monotherapy has been the mainstay of gonococcal infections management for long. But in the face of increasing resistance, and in particular in view of the rise in the number of treatment failures with extended-spectrum cephalosporins (ESC), several countries have recently adopted a dual therapy in their treatment guidelines. In Canada, Europe, South Africa and Australia, where failure with monotherapy has been noticed, the recommended first-line treatment for gonorrhea is Ceftriaxone (250 mg to 500 mg IM) + Azithromycin (1 to 2 g p.o.). However, resistance to Ceftriaxone and Azithromycin have started to emerge globally, and new treatments that tackle Multi-Drug Resistant (MDR) gonorrhea are urgently needed. To address this need, GARDP has partnered with Entasis to support the late development of Zoliflodacin, a new chemical entity with high *in vitro* activity against *N. gonorrhoeae*.

3.3 Zoliflodacin Development history

Zoliflodacin is a first-in-class drug (spiropyrimidinetrione) that inhibits bacterial topoisomerase II and shows in vitro antibacterial activity against several STI pathogens, including *N. gonorrhoeae, C. trachomatis and M. genitalium*. Zoliflodacin follows three other classes of antibacterial agents that target the type II topoisomerases (Fluoroquinolones, novel bacterial topoisomerase inhibitors - NBTIs and Novobiocin). Its mode of action differs from these other classes. *In vitro* data shows that there is no cross-resistance between Zoliflodacin and any other class of antibiotics tested so far. To date, four clinical trials have been completed: a phase I single-ascending dose trial, a phase I Absorption, Distribution, Metabolism, Excretion (ADME) trial, a phase I pharmacokinetic (PK) trial and a phase II study involving patients with confirmed uro-genital gonococcal infection. GARDP is currently planning for the phase III pivotal trial.

3.4 Zoliflodacin Phase 3 Clinical Trial

- **General Information**

- Indication: uncomplicated gonorrhoea
- Study design: a multi-center, randomized, open-label study to assess the safety and tolerability of a single, oral dose of Zoliflodacin compared to up to two comparators
- Participating countries: USA, EU (Netherlands), Thailand, South Africa.
- Subjects: About 1200
- The investigational product (zoliflodacin granules in sachet) and comparator products will be administered to subjects as a single dose

4. SCOPE OF WORK

The current RFP focuses on Clinical Trial Supplies Services to support the conduct of a Phase 3 Clinical Trial in Uncomplicated Gonorrhea.

4.1 Packaging, Labelling and Assembly

- Zoliflodacin will be available as granules in sachets – the primary package – and will required to be labelled by the successful Service Provider as such. The sachets will be manufactured by a CDMO and shipped to the successful Service Provider
- Each Zoliflodacin sachet will be packaged into a secondary carton and labelled accordingly by the successful Service Provider
- Comparator products are required to be purchased by the successful Service Provider from a single, reputable commercial source (manufacturer or wholesaler) and with maximum expiry date.
- The IRT Service Provider will be managed by GARDP
- For EU participating country(ies) (currently only Netherlands planned), the successful service provider will be responsible for organising Qualified Person (QP) certification of the investigational products in compliance with Eudralex Volume 4 Annex 16 and related legislation. The proposal should describe the service provider's arrangements for import and QP certification of Zoliflodacin sachets (ex-US) and comparators (if sourced ex-EU).

4.2 Storage and Distribution

- Service provider is expected to use suitable regional or country depots within their organisation or partner network.
- All third-party depots will be approved by the successful Service Provider and managed accordingly for the purposes of this study
- Shipment of supplies will be distributed to each participating depot, via a shipping agent qualified by the successful Service Provider.
- All aspects of the shipments to the depots, and from depots to participating study sites, will be managed by the successful Service Provider. Logistical support and management of import/export, customs documentation and clearance is expected.
- The successful Service Provider will manage the return and destruction of unused supplies at the depot level only

4.3 Quality Standards

All operations should be conducted in compliance with current EU, USA and national regulatory and statutory requirements, relating to current Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) standards. A Quality Agreement will be established with DNDi which also reserves the right to audit facilities, procedures and related documentation. For supplies used in the EU, QP certification of clinical trial supplies will be required according to EU GMP Annex 16. The selected vendor must commit to permitting an audit, if requested prior to the award of the contract or initiation of any work.

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 GARDP'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 and planning
  - Strategy for supply to proposed clinical trial countries
  - Comparator sourcing strategy
  - Strategy for EU QP certification
  - Experiences/skills, including importation to countries involved in trial, level of company representatives assigned to this project
  - Quality and applicability of proposal presentation
  - Customer testimonials / Experience in related therapeutic area and country

- **Capacity to Deliver**
  - Reasonable timelines
  - Project management capabilities
  - Past experience with similar work
  - Profile of staff involved (CVs)

- **Financial Criteria**
  - Realistic costing of the proposal in Euros with rates consistent with not-for-profit organisations
  - Strategy to ensure efficient allocation/use of investigational products

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
- Technical and financial proposal as described in section 2.3
- Budget with full details of your offer including fixed costs and Pass-Through Costs (Activities performed by subcontractors should be clearly indicated)
- Project Management plan with a detailed description of each activity detailed in section 4.3, plus any underlying assumptions
- Project team involved
- List of tasks and responsibilities
- Project Gantt chart illustrating the timelines for all activities.
- Any other relevant information
- Confidential information will be disclosed after the receipt of the LoI fully signed
- GARDP Technical Service Agreement template will be provided later on the process and comments will be highly recommended if the company will be preselected for bid defences meetings.

6.2 Deliverables

- Summary updates & technical reports
- Purchase of Comparator Products
- Labelled & packaged IMP and Comparator Product with QP certification for EU
- Storage and distribution of IMP and Comparator Products to study sites
- Return and destruction of unused supplies
- Certification

6.3 Timelines

- **GARDP targets to start the study on 15 May 2019, supplies must be ready for distribution three weeks before the start of the study at the latest. The successful Service Provider must be able to comply with these timelines.**
- Timelines for each activity subset should be clearly defined

7. ANNEXES

Annex 1: Intent to participate letter

Annex 2: Q & A Form

Annex 3: Clinical Services Agreement - will be provided when the provider is selected for the bid defence meeting.