Request for Proposal

Regulatory, Site Management and Monitoring Services relative to the pivotal phase III trial supporting registration of Zoliflodacin, in Gonorrhea

Dated: 07 November 2017

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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 endeavoring 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/

1.1. 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 of gonorrhea, 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 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 bacteria.

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 pruritus and/or mucopurulent 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. In pregnant women, the prevalence of gonococcal infections has been estimated at between 3 and 15 % in Low and Middle-Income Countries. Pregnancy complications associated

with urogenital gonorrhea include chorioamnionitis, premature rupture of membranes, preterm birth, ectopic pregnancies and spontaneous abortions.

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, 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 the rising concern of drug-resistant gonorrhea GARDP has partnered with Entasis Therapeutics to develop and register Zoliflodacin, a new chemical entity with high activity against *Neisseria gonorrhoeae*.

1.2.Zoliflodacin Development History

GARDP-Entasis joint development strategy is to register Zoliflodacin with the US FDA and EMA first, and then roll it out to a number of priority countries.

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*, *Chlamydia trachomatis* and *Mycoplasma 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, three clinical trials have been completed: a phase I single-ascending dose trial, a phase I Absorption, Distribution, Metabolism, Excretion (ADME) trial and a phase II study involving patients with confirmed uro-genital gonococcal infection. In the phase II, high cure rates were observed with both the 2000 mg and the 3000 mg dose. The drug was very well tolerated.

GARDP is currently sourcing a Contract Research Organisation (CRO) to assist with US regulatory submissions, US trial sites set-up and management and global monitoring for the pivotal phase III trial supporting registration of Zoliflodacin. Separate Request for Proposals will cover Data Management and Bioanalysis.

CROs are invited to apply to one or more RFPs and proposals will be equally considered by GARDP.

2. RFP INSTRUCTIONS

2.1. General information

a) GARDP invites you as a Service Provider to submit one proposal covering either all or individual 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 service provider's choice following the competitive bidding. GARDP could 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 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 GARDP will consider necessary

f) Late submission proposals are subject to rejection.

g) GARDP 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 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 RFP	GARDP	07 November 2017
Send back the Intent to Participate letter	Service Provider	20 November 2017
Questions sent to GARDP	Service Provider	20 November 2017
GARDP responses to questions	GARDP	15 December 2017
Reception of proposals	Service Provider	31 January 2018
Bidder Pre-selection notification	GARDP	2 March 2018
Bid defense meetings	GARDP	15-16 March 2018
Project award	GARDP	1-2 April 2018
Project Start	Service Provider	Early July 2018

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.

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 Email: cmarty@dndi.org
Technical	Emilie Alirol	Project Leader, Sexually Transmitted Infections (STI)	Phone: +41 22 907 76 06 Email: ealirol@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 GARDP to assess the opportunity of contracting with your company.
- A technical proposal
  - Detailed proposal explaining how your company approach will enable GARDP team to meet project timelines, deliverables and ensure quality results.
- A financial proposal
  - Budget template to be completed for all activities detailed in paragraph 4

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

3.1. Vision & objectives

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 current RFP focusses on clinical services for the Zoliflodacin phase III pivotal trial, however the successful candidate may also be considered for other future studies.

3.2. Projects background

- Indication: Uncomplicated gonorrhea
- Study design: Non-inferiority, parallel, open-label
- Number of participating countries: 4 to 5 countries
- Participating countries/ number of planned sites:
  - South Africa 2-3 sites
  - US 7-10 sites
  - Thailand 3-4 sites
  - European countries 1-2 sites
  - Brazil (TBC) 1-2 sites
  - Additional countries/sites may be considered following feasibility assessment
- Number of randomized patients: 800
- Expected study duration: 15-18 months
- Follow-up duration: 31 days
- Target date for FPFV: Q1 2019
- Target date for LPLV: Q2 2020

4. SCOPE OF WORK

Overall trial management will be under the responsibility of the Project Leader, within GARDP/DNDi headquarters. Close collaboration between the Company, GARDP/DNDi headquarters and Regional Offices is expected and the Company should be able to integrate into the global trial management framework.

For Work Packages 1, 2 and 3, only US is included in the scope of this RFP, the other sites falling under the responsibility of GARDP/DNDi Regional Offices. For Work Package 4, the scope is global.

4.1. Work Package 1: Regulatory Affairs

The Zoliflodacin Phase III trial will include trial sites in the US and will be conducted under a GARDP Investigational New Drug Application (IND). Support is being sought for the following activities:

- Preparation, submission and management of an Investigational New Drug Application (IND) for Zoliflodacin phase III trial.
- Assemble, organize, format and submit amendments and updates under the Zoliflodacin IND. This includes assembling and submitting protocol amendments, Development Safety Update Reports, Annual Reports, Additional chemistry and manufacturing information, investigator brochures updates, etc.
- End-of-trial and study outcome reporting

4.2. Work Package 2: IRB / Ethics Committees Submissions

- Preparation and submission of clinical trial dossiers for ethical review
- Initial submission to central and/or institutional IRBs
- Processing of payments to central and/or institutional IRBs
- Assemble, organize, format and submit amendments and updates
- Draft and submit end-of-study reports

4.3. Work Package 3: Trial Sites set up and management

- Study Start-Up Activities (support in setting up Investigator Site File, Planning and conduct of staff training, initial supplies, etc…)
- Contracts elaboration and negotiation with clinical sites (may be based on bidder's template) and reimbursement of sites costs

4.4. Work Package 4: Global monitoring

- Development of monitoring plan
- Initiation Visit
- Interim Monitoring Visits (ISF review, Drug accountability, AE review and follow-up, ICF review, etc…)
- Regular contacts with investigators through email and/or phone
- Monitoring visit reports by CRA, including:
    - Follow-up of recruitment and follow-up attendance rate
    - Prepare reminders for follow-up visits
    - Follow-up of on-going AEs, medical history, concomitant treatment, pregnancies and births
    - Follow-up of on-going SAEs
    - Follow-up and resolve open action items identified during monitoring visits
- Maintenance of ISF and updating of corresponding trackers
- Management of supplies (IMP, medical material, non-IMP, etc)
- Close-out Visit
- Query Resolution and third-party data reconciliation issues
- Root-cause analysis of identified problems and preparation of corresponding response plans

	STI Program
CRF type	electronic
Expected number of CRF pages	40
Expected average number of monitoring visits (per site)	5-8
Expected total number of SAEs	≤20

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 total cost of the offer.

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

5.1. Technical criteria

- Project approach, methodology 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

5.2. Capacity to deliver

- Ability to meet GARDP timelines
- 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

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
- Budget with full details of your offer including fixed costs and Pass-Through Costs. The activities that your company plans to outsource need to be clearly identified.
- Project team involved
- List of tasks / responsibilities and project management plan
- 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

- Beginning of Services planned in July 2018
- Timelines for each activity subset should be clearly defined
- Completion of Services in December 2020 at the latest.

6.3. Additional information

Within the context of the development of both projects, GARDP is launching other RFP for the different services needed. Although this RFP refers specifically to Regulatory Affairs, Site Management and Monitoring, candidates are allowed to apply to more than one service as long as different proposals are submitted in compliance to each of the RFP.

7. ANNEXES

Annex 1: Intent to Participate letter

Annex 2: Q & A Form