Request for Proposal

International courier services to support the conduct of a phase 3 clinical trial in uncomplicated gonorrhoea and neonatal/paediatric programmes

Dated: 26 November 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 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/
GARDP plans to conduct a multi-center, randomized, open-label, non-inferiority trial to evaluate the efficacy and safety of a single, oral dose of zoliflodacin compared to a combination of a single, intramuscular dose of ceftriaxone and a single oral dose of azithromycin in the treatment of patients with uncomplicated gonorrhoea. GARDP is also running a neonatal and paediatric programme involving a number of clinical studies globally. GARDP is sourcing an international courier offering clinical samples shipment services to support such programmes, with the intention of setting up a master service agreement with the courier for several years for all future programme needs

1.1. Uncomplicated gonorrhoea

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 gonorrhoea, 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 gonorrhoea. *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 gonorrhoea 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 intra-muscular) + azithromycin (1 to 2 g oral). However, resistance to ceftriaxone and azithromycin have started to emerge globally, and new treatments that tackle multi-drug resistant (MDR) gonorrhea are urgently needed. As part of its STI program, GARDP is planning a multi-national, multi-center phase III trial to assess the efficacy and safety of zoliflodacin for the treatment of uncomplicated gonorrhoea.

1.2.Neonatal Sepsis

The spread of antimicrobial resistance (AMR) is an urgent, global threat, raising the spectre of a world without effective antibiotics. Among the initiatives being planned to prevent (or at least control) such a crisis, special attention is required for newborn babies (neonates), since their immune system is not yet fully developed, and they are therefore particularly vulnerable to infection.

Despite progress on child mortality, neonatal mortality remains unacceptably high. Nosocomial infections are the leading cause of mortality and morbidity in the neonatal intensive care unit (NICU), affecting from 7% to 24% of admitted patients. In all hospital settings, especially NICUs, the increase of infections caused by MDR Gram negative bacteria resistant to antibiotics (including carbapenems) represents a serious threat, especially for critically ill neonates who are at high risk due to the immaturity of their immune systems. Since few new antibiotics are under development, there has been renewed interest in optimising the use of polymyxins including Colistimethate sodium (CMS, pro-drug of colistin) and polymyxin B (PMB).

Polymyxin antibiotics (colistin (polymixin E) and polymyxin B) have been increasingly used as last-line treatment for *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* infections resistant to other available antibiotics. Since their marketing approval was in the 1950s, these drugs were not subjected to modern drug development procedures and information on their clinical use are scarce. Different formulations are available worldwide. For CMS product vials may be labelled as international units (IUs) of pro-drug, mg of pro-drug or mg of colistin base activity (CBA), the active drug. There is no general consensus on the standard dosing of colistin globally. Polymyxin B is the active drug, so dosing is simpler, however recommendations for adult dosing of either drug (CMS or PMB) are based on a limited literature and particularly lacking are high quality PK studies in critically-ill patients.

These are even more critical issues in the neonatal population, especially those severely ill, who have very different PK characteristics compared to children and adults. Indeed, while for critically-ill adults the key colistin PK parameters after CMS or PMB IV administration have been studied, in critically neonates these are largely unknown, and the reported doses used internationally vary widely. In neonates, for CMS there is the added complexity of the immature renal and hepatic enzyme function, including the enzymes that hydrolyse CMS.

There is therefore a clear need to conduct a prospective pharmacokinetic study evaluating PMB and CMS for defining the optimal dosing regimen in neonates.

2. RFP INSTRUCTIONS

2.1. General information

a) GARDP invites you as a service provider to submit one proposal covering all services described in Section 3

b) This entire request for proposal (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. Those terms and conditions are non-negotiable.

c) All bidders are required to complete and return the intent to participate letter.

d) The issuance of this RFP 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	26 November 2018
Send back the intent to participate letter	Service provider	7 December 2018
Questions sent to GARDP	Service provider	14 December 2018
GARDP responses to questions	GARDP	21 December 2018
Reception of proposals	Service provider	25 January 2019
Bidder pre-selection notification	GARDP	4 February 2019
Bid defense meetings	GARDP	11 February 2019
Project award	GARDP	25 February 2019
Project start	Service provider	May 2019

2.3. RFP processes and contact information

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 prior to the submission of technical proposal, in line with the timelines outlined in Section 2.2. To submit your questions, please use the form attached as Annex 2.

In order to ensure 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.

Questions types	Contact person	Title	Contact information
Contractual	Christophine Marty Moreau	Senior Procurement Manager	Phone: +41 22 906 9261 Email: cmarty@dndi.org
Technical	Jessica Renaux	Clinical trial manager	Phone: +41 79 137 8281 Email: jrenaux@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

2.5.Conflict of interest

The company shall disclose any actual or potential conflicts of interest in the intent to participate letter.

3. SCOPE OF WORK

Shipment of various biological samples in a range of conditions. Details for the **zoliflodacin phase 3 study** are presented in the table below:

Sample type	Container type	Approximate number of samples per shipment	Conditions	Country of origin	Country of destination	Predicted timelines
Plasma	4 ml polypropylene tube	150	Frozen, dry ice	Thailand	USA	1 to 3 (to be determined) shipments per location between November 2019 and November 2020
		150		South Africa		
		50		Netherlands		
		25		USA, 5 different locations		
Bacterial isolates	2 ml vials	500	Frozen, dry ice	Thailand	USA	4 shipments per location: November 2019 February 2020 June 2020 November 2020
		400		South Africa		
		100		Netherlands		
		300		USA, 5 different locations		
Bacterial isolates	2 ml vials	3500	Frozen, dry ice	USA	Sweden	1 shipment: March 2021
Urine	30 ml urine collection pots	100	Frozen, dry ice	Thailand	USA	10 shipments: approximately every 2 months (July 2019 – December 2010)

For all countries and sample types, a test shipment may be performed in advance of project deliverables.

Neo Poly B 001 study

Sample type	Container type	Approximate number of samples per shipment	Conditions	Country of origin	Country of destination	Predicted timelines
Polymyxin B	Glass vials size TBC (approx. 50ml)	30-50	Ambient	Denmark (TBC)	Italy, Greece, South Africa	1 shipment per location: Q4 2019/Q1 2020
Plasma/CSF	4 ml polypropylene tube	80	Frozen, dry ice	Italy	TBD (Europe /Australia)	2 shipments per location: During 2020
		80		Greece		
		160		South Africa (2)		
Bacterial isolates	2 ml vials	20	Frozen, dry ice	Italy	Europe	1-2 shipments per location: During 2020
		20		Greece		
		40		South Africa (2)		

Other GARDP projects will also require international courier services for shipment of clinical / microbiological samples in frozen conditions, as well as investigational product, reagents and laboratory consumable/kits as required from/to countries including – but not limited to – Italy, Greece, South Africa, India, Belgium, Kenya during 2020 and 2021. Details of such services will be shared with the selected service provider in due course as projects develop. For the purpose of this RFP, please provide any cost estimate that might be relevant to the above-mentioned activities.

4. 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:

4.1. 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 countries
- Compliance with US FDA, EMA, Thai FDA and SAHPRA requirements

4.2. Capacity to deliver

- Ability to meet GARDP timelines
- Project management capabilities
- Past positive experience with similar activities

4.3. Financial criteria

- Realistic costing of the proposal with NGO rates whenever possible
- Price list to be fixed during the duration of the MSA

5. PROPOSAL REQUIREMENTS & TIMELINES

5.1. 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
- Technical and financial proposal as described in section 2.4
- Budget with full details of your offer, including individual costs and timelines for each shipment site
- Project team involved
- List of tasks / responsibilities
- Any other relevant information

5.2. Timelines

- Beginning of services planned in May 2019 for the 1st study Zoliflodacin Phase 3 study
- Completion of services for the phase 3 clinical trial in December 2020
- Completion of involvement for other projects to be determined

6. ANNEXES

Annex 1: Letter of Intent to participate template

Annex 2: Q&A form