Request for Proposal

Clinical Supply services related to the following study:

Phase 4 public health trial in clinically diagnosed neonatal sepsis (NeoSep1)

Dated: October 19th, 2021

Content

1. PURPOSE

GARDP Foundation ("GARDP") is a not-for-profit organization developing new treatments for drug-resistant infections that pose the greatest threat to health. GARDP works with partners to ensure sustainable access to treatments, promoting responsible use and affordability to all in need. Created by the World Health Organization (WHO) and Drugs for Neglected Diseases initiative ("DNDi"), GARDP is essential to delivering on the Global Action Plan on Antimicrobial Resistance. GARDP's goal is to partner with governments and treating physicians in low- and middle- income countries (LMIC) to bring fit for purpose solutions to the bedside of patients, that would save lives as well as promote the responsible use of antibiotics. GARDP operates with an international network of offices supporting the mission of GARDP including DNDi GARDP Southern Africa NPC and DNDi regional offices that carry out activities in support of the GARDP mission.

GARDP is sourcing a CRO able to supply clinical IMPs to the different sites of the following clinical trial; An open label randomized controlled trial to compare new and existing combination antibiotic regimens for treating clinically diagnosed neonatal sepsis (Part 2) with a run-in confirmatory pharmacokinetic phase (Part 1) to rank novel and existing combination antibiotic regimens for treating proven or suspected multidrug resistant neonatal sepsis.

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

1.1.Neonatal Sepsis burden and treatment

There is a high burden of disease of neonatal sepsis globally but especially in LMICs.

In 2018, WHO estimated 2.5 million deaths in neonatal period (0-1 month), mostly in LMICs. 15% of neonatal deaths attributed to sepsis, infections being 3rd most common cause of neonatal deaths (2018: 400,000 neonatal deaths due to infection).

The Current WHO guidelines recommendations for treatment of neonatal sepsis are:

- First line -Intravenous Ampicillin (or benzyl penicillin) and Gentamicin Second line – Intravenous cefotaxime or Ceftriaxone

Other commonly used antibiotics:

- Amikacin 250mg/ml Injection
- Piperacillin/tazobactam
- Meropenem

1.2.Empiric treatment Development history

GARDP has assessed a number of off-patent antibiotics that have an established neonatal dose to identify those that could be taken forward into such a trial. The antibiotics identified that met the criteria to be taken forward into the clinical trial were fosfomycin (40mg/ml injection), flomoxef, in combination with each other or amikacin.

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 and summarized below.

Programme	Type of Trial	Services to be provided
NeoSep 1 study part 1	PK and safety evaluation of fosfomycin and flomoxef when given as a novel combination regimen	- Packing - Over labelling - Assembly of IMP (Flomoxef & Fosfomycin) -Distribution of IMP to study sites
NeoSep 1 study part 2	Open label parallel group randomised trial comparing combinations of fosfomycin flomoxef and amikacin and multiple standard of care antibiotic regimens.	- Packing - Over labelling - Assembly of IMP - Storage & distribution - Sourcing of 2 standard antibiotics

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 Letter attached as Annex 1.

c) All bidders are required to complete and send back 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	October 22nd 2021
Send back the LoI	Bidders	October 29th 2021
Provide the study synopsis	GARDP	November 1st 2021
Questions sent to GARDP	Bidders	November 5th 2021
GARDP responses to Q&A	GARDP	November 12th 2021
Receipt of proposals	GARDP	November 26th 2021
Bidder Preselection notification	GARDP	January 6th 2022
Bid defence meetings	GARDP & bidders	January 20th 2022
Project award	GARDP	February 1st 2022
Project Start	Service Provider	March 2022

2.3. RFP processes and contact information

2.3.1. Confirmation of Intent

Please transmit your intent to participate letter (LoI) 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).

Please note the "Intent to participate letter" is a standard document which GARDP cannot afford negotiating due to project priorities, time and resources dedication. This template is based on several years of experiences working with services providers and contains widely acceptable terms.

2.3.2. Questions

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.

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	Antony Simon	Pharmaceutical Development Manager	Phone: +41 22 907 78 94 Email: asimon@gardp.org
	Cc: Karin Hergarden	Clinical Research Manager	Phone: +41 22 555 1966 Email: khergarden@gardp.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 to be provided for all activities detailed in section 4

2.5.Conflict of Interest

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

3. NEONATAL SEPSIS PROGRAM OVERVIEW

GARDP R&D strategy for Neonatal sepsis aims at delivering, an affordable 'empirical' treatment for neonatal sepsis and meningitis in settings with high resistance rates to the WHO first line empiric therapy of ampicillin and gentamicin, where the pathogenic bacteria have not been formally identified.

The objective of the GARDP Neonatal sepsis project is to meet the public health needs to identify novel regimens from existing generic antibiotics that provide broader coverage against multi-drug resistant pathogens to improve clinical outcomes for neonatal sepsis globally.

3.1. Background and general information

Indication	Clinically diagnosed neonatal sepsis
Study design	Part 1 : Sequentially enrolling 3 cohort PK study
	Part 2 : An open label randomized controlled trial to rank novel and existing combination antibiotic regimens for treating proven or suspected multidrug resistant neonatal sepsis
Participating countries	Bangladesh or Pakistan (1 site), Kenya (2 – 3 sites); South Africa (3 sites), Uganda (2 sites), DRC (Democratic Republic of Congo) or Nigeria (1 site), India (3 sites), Brazil (2 sites), Tanzania (1 site), Vietnam (1 site)
	Approximately 10 countries, 20 sites
Subjects	Part 1 : 60 babies
	Part 2 : approximately 3000 babies
Expected study duration	36 – 42 months both parts
Follow up duration	90 days after randomization
Target date FPFV	Part 1 : May 22

	Part 2 : Mar 23
Expected DB lock	Q2 2027
Expected analysis and CSR	Q3 2027
Clinical supplies	Part 1: - Flomoxef 1 g - Fosfomycin 2 g or 4g Part 2: - Flomoxef 1 g - Fosfomycin 2 g or 4g - Current treatment regimens

4. SCOPE OF WORK

Overall trial management will be under the responsibility of the Project Leader and the Clinical Trial Manager, within GARDP headquarters. Close collaboration between the Company, GARDP headquarters and Regional Offices in East Africa, South Africa and Southeast Asia is expected, and the Company should be able to integrate into the global trial management framework.

The current RFP focuses on Clinical Trial Supplies Services to support the conduct of the clinical trial. Due to the target population (neonates hospitalized with clinical signs of neonatal sepsis), the study team will aim to select sites in secondary (smaller, non-departmentalized hospitals including emergency and regional hospitals) and tertiary health facilities (Technological and sophisticated services offered by medical centres and large hospitals).

4.1. NeoSep Part 1

4.1.1. Packaging, Labelling & Assembly

- <u>Flomoxef and Fosfomycin</u>
    - Flomoxef and Fosfomycin will be manufactured by pharma partner and shipped to the Service Provider (one shipment per drug)
    - Flomoxef will be available as 1 g Vial bottle – primary package in Japanese– and will required to be labelled/ over labelled by the service provider in one different language (English). Each Flomoxef vial will be packed into a secondary carton and labelled/ over labelled accordingly by the Service Provider. Flomoxef 1 g vials should be stored under controlled low temperature conditions at 5ºC when it is distributed in a tropical climate zone.
    - Fosfomycin will be available as 2 g vial - primary package in English - and will required to be over labelled by the service provider in English. 10 Fosfomycin 2 g vials will be packed into a secondary carton and over labelled accordingly by the Service Provider. Fosfomycin 2 g vials should be stored at ambient conditions 15 - 25°C.
    - One labelling/packaging run per drug is expected.

- Development of a single label language in English for flomoxef and fosfomycin vials and cartons. Flomoxef and Fosfomycin vials and cartons labels text will be provided by GARDP in English.
- The Service Provider will manage according to the regulations and facilities at site, the return and destruction of unused supplies at the depot level only (2 sites in South Africa and 1 site in Kenya)
- Addition of clinical trial specific label requirements in English for fosfomycin and flomoxef (IMP)
- QP services in case of EU based vendors

4.1.2. Storage and distribution

- Shipment of supplies will be distributed to each participating sites (one site in Kenya, Kiliffi and two sites in South Africa, 1 in the western cape and 1 in Johannesburg), via a shipping agent qualified by the Service Provider through suitable regional or country depots if required, at controlled temperature conditions. Shipment will be accompanied by a temperature monitoring device.
- One shipment of supplies per site is expected.
- All aspects of the shipments to the participating study sites, will be managed by the Service Provider. Logistical support and management of import/export, customs documentation and clearance is expected.

4.1.3. Estimated needs for part 1

	No patient	**No vials**
Fosfomycin	40	560
Flomoxef	40	840

Service providers should describe their assumptions regarding overages and their strategies for minimising them.

4.2. NeoSep Part 2

4.2.1. Packaging, Labelling & Assembly

- <u>Flomoxef and Fosfomycin</u>
  - Flomoxef and Fosfomycin will be manufactured by pharma a partner and shipped to the Service Provider (four shipments per drug are estimated)
  - Flomoxef will be available as 1 g Vial bottle – primary package in Japanese– and will required to be labelled/ over labelled by the service provider as such. Each Flomoxef vial will be packed into a secondary carton and labelled/ over labelled accordingly by the Service Provider. Flomoxef 1 g vials should be stored under controlled low temperature conditions at 5ºC when it is distributed in a tropical climate zone.

- Fosfomycin will be available as 2 g or 4 g vial - primary package in English - and will required to be labelled/ over labelled by the successful service provider as such. 10 Fosfomycin 2 g or 4g vials will be packed into a secondary carton and over labelled accordingly by the successful Service Provider. Fosfomycin 2 g or 4g vials should be stored at ambient conditions 15 - 25°C.
- Two labelling runs per drug are expected to accommodate the expiry date of the batches provided.
- Development of a multi-language label booklet (assumed: French, Portuguese, Vietnamese and English). Flomoxef and Fosfomycin vials and cartons label text will be provided by GARDP in English. Translation should be performed by the service provider.
- QP services in case of EU based vendors

Optional: Meropenem and Piperacillin/Tazobactam:

Routinely used antibiotics will be sourced locally. However, potentially two comparator products are expected to be sourced by the Service provider (Meropenem & Piperacillin/tazobactam) from a reputable commercial source (manufacturer or wholesaler) with a maximum expiry date.

Meropenem:

Meropenem 500 mg powder for solution for injection or infusion: Dry powder should be stored at controlled room temperature 20°C to 25°C

Piperacillin/Tazobactam:

- Piperacillin/Tazobactam 4g/0.5g Powder for Solution for Infusion. This medicinal product should not be stored ≤ 25°C Two over labelling runs per drug are expected to accommodate the expiry date of the comparator batches sourced.
- Development of a multi-language label booklet (at least four different languages, assumed: French, Portuguese, Vietnamese and English). Meropenem and Piperacillin/Tazobactam vials and cartons label text will be provided by GARDP in English. Translation should be performed by the service provider.

4.2.2. Storage & Distribution

- The 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 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 Service Provider at controlled temperature conditions. Shipment will be accompanied by a temperature monitoring device.
- All aspects of the shipments to the depots, and from depots to participating study sites, will be managed by the Service Provider. Logistical support and management of import/export, customs documentation and clearance is expected.

- The Service Provider will manage according to the regulations and facilities at site, the return and destruction of unused supplies at the depot level only (GARDP assumes around 2 – 3 sites/ participating country/ region).

4.2.3. Estimated needs for part 2

4.2.3.1 IMP part 2

The tables indicate a need estimation for part 2 of the study:

Fosfomycin	No **sites**	≈ No **patients**	No vials/ trt	≈ No **pat 1st line**	No **vial 1st line**	No **vials** 2nd line	**Overage**	**Total**
	20	3500	14	1021	14300	4288	4645	23220

Flomoxef	No **sites**	≈ No **patients**	**# vials/ trt**	≈ No pat **1st line**	No **vials** 1st line	No **vials** 2nd line	**Overage**	**Total**
	20	3500	21	1021	21500	6431	8361	36230

4.3.2.2 Needs of standard medication for part 2

Routinely used antibiotics will be sourced locally. However, as stated above potentially two comparator products are expected to be sourced by the Service provider (Meropenem & Piperacillin/tazobactam). GARDP assumes at present, that the regions to be provided with additional standard treatment are:

- Bangladesh or Pakistan
- Kenya
- Uganda
- DRC or Nigeria
- Tanzania

Standard Medication	No **of sites**	≈ No **patients**	No vials **per trt**	**Total**
Meropenem	10	400	21	8400
Piperacillin/Tazobactam	10	400	21	8400

The number of vials for the standard of care drugs Meropenem and Piperacillin/Tazobactam are rough estimates, since the randomization for part 2 of the protocol is personalized. The standard treatment dependents highly on the treatment protocols in various countries (see section 3.1) participating.

4.3.Quality standards and insurance

All operations should be conducted in compliance with current EU or other regulations (depending on the location of the successful Service Provider and the selected sites) 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 GARDP which also reserves the right to audit facilities, procedures, and related documentation. For supplies from 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 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 March 2022

- Timelines for each activity subset should be clearly defined

Programme	Type of Trial	Number of Countries	Number of Sites	Planned Start
NeoSep1 part 1	PK and safety evaluation of fosfomycin and flomoxef when given as a novel combination regimen	2	3	Late Q1 2022
NeoSep1 part 2	Open label parallel group randomised trial comparing combinations of fosfomycin flomoxef and amikacin and multiple standard of care antibiotic regimens.	10	18-20	Q1 2023

- Completion of Services is assumed for Q2 2026.

7. ANNEXES

Annex 1: Intent to Participate letter template (LoI)

Annex 2: Q & A Form

Annex 3: NeoSep1 Synopsis will be shared after the receipt of the LoI duly signed