Request For Proposal

A Phase 1, Single-Dose, Open-Label, Randomized, Crossover Bioequivalence Study of 3 g Zoliflodacin in Healthy Adult Volunteers

Dated: July 2019

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1. PURPOSE

1.1 GARDP mission

The Global Antibiotic Research and Development Partnership (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 their sustainable access.

Initiated by the World Health Organization (WHO) and the Drugs for Neglected Disease initiative (DNDi) in May 2016, GARDP is an important element of WHO's Global Action Plan on Antimicrobial Resistance that calls for new public-private partnerships to encourage research and development of new antimicrobial agents and diagnostics. GARDP became its own legal entity ("The GARDP Foundation") in July 2018 and was incubated by DNDi until March 2019.

During its incubation, and through the generous support of donors and partners, GARDP has built a skilled and dedicated team with expertise from a range of sectors and backgrounds led by a Board of Directors comprising leading international experts in the global health arena.

In the last three years, GARDP has formed numerous partnerships with industry, academia and research institutions in support of its clinical programmes to develop antibiotics for drug-resistant infections for children, newborns with sepsis, and sexually-transmitted infections. These collaborations span the drug development lifecycle and include screening chemical libraries for antibacterial activity, assessing the viability of potential antibiotic candidates, and the completion of three clinical trials.

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

1.2 Sexually Transmitted Infections Program

GARDP R&D strategy for Sexually Transmitted Infections (STI) 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.

1.3 Zoliflodacin

In July 2017, Global Antibiotic Research & Development Partnership (GARDP) partnered with Entasis to develop zoliflodacin, a novel bacterial type-II topoisomerase inhibitor from the spiropyrimidinetrione class, in late-stage clinical development.

Zoliflodacin has demonstrated activity in vitro against N. gonorrhoeae, including drug-resistant strains. To date, 5 clinical studies have shown that Zoliflodacin has the potential to be a safe, effective (high cure rates level for urogenital and rectal infections) and convenient single dose oral treatment of uncomplicated gonorrhoea. Currently, a non-inferiority phase 3 study is about to start to assess the efficacy and safety of zoliflodacin against uncomplicated gonorrhoea globally.

For the late stage clinical trials, zoliflodacin has been manufactured as a granule form for oral suspension formulation. In parallel, development and scale-up for registration and commercial production is being performed by another vendor. The proposed commercial drug product will be granules with the same qualitative-quantitative composition as the granule investigational product.

2. RFP INSTRUCTIONS

2.1 General information

a) GARDP invites you as a Service Provider to submit one proposal covering the services described in Section 3.

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 RFP	GARDP	July 19th 2019
Send back the Intent to Participate letter	Service Provider	July 25th 2019
Send the synopsis to Service Provider	GARDP	July 29th 2019
Q&A sent to GARDP	Service Provider	August 5th 2019
GARDP responses to Q&A	GARDP	August 8th 2019
Reception of proposals	GARDP	August 22nd 2019
Notification to preselected bidders	GARDP	August 29th 2019
Bid Defence Meetings	GARDP / Service Provider	September 10th 2019
Award notification	GARDP	September 19th 2019

2.3 RFP processes and contact information

2.3.1 Instructions

All bidders may request further clarifications in regards of this current RFP, by addressing questions in writing to the dedicated key contacts identified below. These questions should be submitted to GARDP at the date mentioned in the section 0 of the RFP.

In order to keep a fair bidding process, questions on the drugs to be assessed will only be answered in a document shared with all the bidders on the date indicated in section 0 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 GARDP cannot afford negotiating due to project 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 and Sophie Delhomme (contacts details below).

Questions types	Contact person	Title	Contact information
Contractual & Financial aspects	Christophine MARTY MOREAU	Senior Procurement Manager	15 Chemin Louis Dunant, 1202 Geneva, Switzerland Phone: +41 22 906 92 61 Email: cmarty@dndi.org
Technical aspects	Sophie Delhomme	Senior Clinical Manager	Email: sdelhomme@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 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 as detailed in section 2.1
  - Acceptance of GARDP agreement template: Clinical Trial Agreement will be provided at a later stage of the process.

- **A technical proposal**
  - Detailed proposal explaining how your company approach will enable GARDP team to meet project timelines and insure quality results.

- **A financial proposal**
  - Budget template to be completed and attached as Annex 3.

- **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.

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

The objective of this RFP is to assess the bioequivalence of zoliflodacin administered as 3g oral dose of test product and 3g oral dose of reference product, in fasting and [specific] fed conditions in healthy adult's volunteers.

In addition, the safety and tolerability of both products will be evaluated. Also, the effect of food on the PK of zoliflodacin in healthy male and female subjects for both the reference and the test products will be investigated.

The study will consist of a screening phase and a treatment phase, during which subjects will be randomly (1:1) allocated to either group A or B for cohort 1 (fasting) or to group C or D for cohort 2 ([specific] fed condition). All subjects will receive 1 single doses of each zoliflodacin formulation (reference and test) in a cross over fashion separated by an expected washout period of 3 to 5 days.

Cohort 1 (Fasting condition, 18 subjects):

- Group A: Subjects will receive in period 1, the test product and in period 2 the reference product in a crossover fashion.
- Group B: Subjects will receive in period 1, the reference product and in period 2 the test product in a crossover fashion.

Cohort 2 ([specific] fed condition, 18 subjects):

- Group C: Volunteers will receive in period 1, the test product and in period 2 the reference product in a crossover fashion.
- Group D: Volunteers will receive in period 1, the reference product and in period 2 the test product in a cross-over fashion.

All subjects will receive 2 single doses of zoliflodacin (both formulations) separated by an expected washout period of 3 days minimum.

GARDP will provide the IMPD, Investigator Brochure, Clinical Study Synopsis, and packaged IMP.

3.1 Phase I Clinical trial: Key data

Indication: Uncomplicated gonorrhea

Study design: This is a Single-Dose, Parallel, Open-Label, Randomized, two-period, two-sequence, two-treatment, Crossover Bioequivalence Study of zoliflodacin administered as 3g oral dose of test product and 3g oral dose of reference product , under fasting and [specific] fed conditions.

Primary objective of the study: The objective of the present study is to compare in healthy volunteers, under fasted and [specific] fed conditions, the pharmacokinetic (PK) properties (rate and extent of absorption) of zoliflodacin when administered as a single 3g oral dose of the test product or as a single 3g oral dose of the reference product.

Secondary objective of the study: The secondary objectives of the study is to evaluate the safety and tolerability of the single 3g oral doses of zoliflodacin in healthy volunteers from the reference and the test products., and, to evaluate the effect of food on the PK of zoliflodacin in healthy male and female subjects for both the test and the reference products.

No. of participating countries: 1 country (in Europe or in the USA)

Participating clinical sites: 1 site

Note: fed conditions are referred as [specific] fed conditions and will be defined at the protocol stage: low, intermediate or high fat/calorie standardized meal.

3.2 General Information on the study

3.2.1 Main criteria for inclusion

Healthy non-smoker men and women, aged 18 to 55 years; body mass index (BMI) in the range 18 to 30.1 kg/m^2 at screening; deemed healthy on the basis of medical history and physical examination, electrocardiogram (ECG), vital signs, clinical laboratory evaluations; agree to follow the contraception requirements of the study and give fully informed written consent to participate in the study.

3.2.2 Study duration

Each volunteer completing the trial will be evaluated over study participation for a maximum period of 48 days, including a 27-day screening period (Day-28 to Day -1), two 3 days/2 nights confined residential period, a 3-5 days washout period and a 7-10 days follow-up period after the last residential period.

3.2.3 Study design and procedures/assessments

Up to 18 subjects will be enrolled per food regimen. Therefore, a total of 36 subjects will be enrolled for the whole BE study.

All subjects will receive 1 single doses of each formulation of zoliflodacin (test and reference products) separated by an expected washout period of 3 days minimum.

Subjects who are in a period in which they are fed will be dosed 30 minutes after the start of the meal. The volunteers are expected to consume the entire meal within the 30 minutes prior to dosing).

Eligible healthy volunteers will come to the Clinical Study Unit in the late afternoon/evening of Day -1 (the day before the first dose of study medication).

On Day 0, the healthy subjects will receive in a randomized fashion (1:1), a single oral dose of zoliflodacin as suspension in water, under fasted or [specific] fed conditions.

Intensive PK sampling and clinical and laboratory safety monitoring will be conducted post-dose during Days 0-2 (please see schedule of events). Healthy volunteers are expected to remain at the research facility until the 48-hour post-dose PK sample is obtained and safety assessments (on Day 2 evening) are performed.

Subsequently, after a washout period (Days 3-5), healthy subjects will return to the Clinical Study Unit in the late afternoon/evening of Day 6 to be re-confined for receipt of their second zoliflodacin dose on Day 7

Intensive PK sampling and clinical and laboratory safety monitoring will be conducted post-dose during Days 7-9 (please see schedule of events). Healthy volunteers are expected to remain at the research facility until the 48-hour post-dose PK sample is obtained and safety assessments (on Day 9) are performed.

A safety follow-up visit will be conducted on Day 16-19 days of the last period, or at the time of early termination (if applicable)

3.2.4 PK sampling

Blood sampling:

- For each subject under fasting conditions, blood will be collected at the following time points: pre-dose and 0.5, 1.0, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 9.0, 12.0, 24.0 and 48.0 h post-dose (PK sampling 1 and 2).
- For each subject under [specific] fed conditions, blood will be collected at the following time points: pre-dose, and 0.5 ,1.0, 2.0, 3.0, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 9.0, 12.0, 24.0, 48.0 h post-dose (PK sampling 3 and 4).

3.2.5 Statistical considerations

As recommended by FDA (Guidance for Industry "Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs -General Considerations and "Food-Effect Bioavailability and Fed Bioequivalence Studies", 2002) 12 subjects should complete the study, to achieve adequate power for a statistical assessment of Bioequivalence.

Assuming that 25% of the subjects with have unevaluable PK data, a total of 18 subjects will be enrolled per cohort and therefore 36 for the whole study.

3.3 List of activities to be performed

- Protocol writing
- Volunteer Information Sheet and Informed Consent Form development
- Regulatory and Ethics Committee submissions
- Case Report Form (CRF) design (please include both paper and eCRF options if currently in use by Service Provider)
- Storage and management of IMP, including accountability and return to sponsor or designee (please also include an option to destroy IMP onsite or through 3rd party)
- Pharmacy manual development
- Technical input on labelling as per local requirements (validation of labels proposed by Sponsor ahead of labelling procedure)
- Randomization
- Clinical trial conduct: subject recruitment, screening, dosing, and all clinical procedures detailed in section 4.1. and final synopsis, including Holter monitoring
- Biometrics (database design, data entry, data management, data cleaning, and statistical analysis)
- Project Management of activities conducted by the Service Provider, including required plans for the activities where applicable (e.g. DMP, Monitoring Plan, SAP etc.)
- Clinical Trial Monitoring (including Monitoring Plan preparation)
- PK Analysis: Service Provider will prepare the plasma samples and ship them to a third-party contracted by GARDP for the bioanalysis (laboratory in US). Data to be transferred back to the Service Provider for data analysis.
- Storage of PK back-up samples and plasma left-over (frozen) up to the end of the study (up to a maximum of 3 months after the end of the study) – Capacity to destroy the samples after written approval of the Sponsor
- Pharmacovigilance: Managed by GARDP – forms to be provided by GARDP
- Investigator Site Documentation

3.4 Expected reporting

- Study Status Reports (weekly): start-up progress, recruitment, data cleaning and AE log
- Meetings: weekly telephone meetings with the Sponsor, kick-off meeting
- Clinical Study Report writing (2 drafts, one final)
- Database and other documents transferred to Sponsor (on CD-Rom or equivalent electronic support at the end of the study).

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 cost of the offer.

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

4.1 Technical criteria

- ✓ Facilities and license to perform both studies in compliance with CFR part 11
- ✓ Records of Audits/Inspections of the facilities/processes

4.2 Capacity to deliver

- ✓ Reasonable timelines including at least but not only the ones related to recruitment, and regulatory and EC submissions, subject recruitment, samples shipment, availability of reports. Please specify projected timelines in the proposal, including 'best case' and 'worst case'.
- ✓ Project management capabilities and experience
- ✓ Experience with similar work
- ✓ Experience with GARDP/DNDi
- ✓ Profile of staff involved (CVs)

4.3 Financial criteria

- ✓ Realistic costing of the proposal with NGO rates when possible.

5. PROPOSAL REQUIREMENTS, DELIVERABLES & 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 2.1
- ✓ Technical and financial proposal as described in section 2.4. Budget with full details of your offer including fixed costs and Pass-Through Costs. We recommend the use of GARDP template inserted as Annex 3.
- ✓ Whole project timelines including Regulatory and Ethics submission and approval (taking into account holiday period as applicable)
- ✓ Project team involved
- ✓ List of tasks and responsibilities.

In addition, please provide us with complementary information on:

- ✓ Standard QA package recommended by the Service Provider (e.g. audits, QC procedures etc.)
- ✓ Proposals for monitoring scope and schedule
- ✓ Options to front-load activities in order to gain time (e.g. pre-screening)
- ✓ Service Provider facilities for re-labelling (following shelf life extension) if required
- ✓ Phase I unit's pharmacy capabilities (potential IMP preparation, dispensation, full accountability)
- ✓ Database, including details of transfer to Sponsor and corresponding costs

5.2 Deliverables

- ✓ Protocol
- ✓ ICF
- ✓ Pharmacy Manual
- ✓ eCRF/CRF, database specifications and edit-checks, CDisc format
- ✓ Regulatory and IRB(s) approvals
- ✓ Monitoring reports
- ✓ Data management report
- ✓ Complete package of TMF documentation, for all activities managed by the Service Provider
- ✓ Final Clinical Study Report
- ✓ Database transfer

6. ANNEXES

Annex 1: Intent to Participate letter

Annex 2: Q & A Form

Annex 3: Budget template

Annex 4: Final synopsis, to be provided by July 29th

Annex 5: Clinical Trial Agreement template, to be provided at a later stage