GARDP Sexually Transmitted Infections Program

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Committee on Prevention and Control of STI in the United States
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GARDP - an innovative model and approach

Notably, the flexible and unique model allows GARDP to

- Work from any entry point along the R&D pipeline through to patient access.
- Target important indications less likely to be developed by other actors.
- Ensure access and stewardship of products developed by GARDP in contractual agreements with the private sector.
- Invest funding in programmes driven and directly executed by GARDP and our partners.

GARDP
In-house:
- public health expertise
- product development & clinical trial know-how

Partners
- Academia
- Civil society/NGOs
- Research institutions
- Pharma/biotech
- Government/international organizations

The way we work
- Prioritize public health needs
- End to end
- Develop TPPS & scientific road maps
- Embed appropriate use & access
- In- and out-licensing, generics
- Sponsors, research studies & clinical trials
Executive Summary

Ambition

Vision
All infections are treatable for everyone, everywhere

Mission
Bring together the public and private sectors to develop new treatments for bacterial infections. We ensure responsible and sustainable access, addressing the public health impact of antibiotic resistance

GARDP Strategic Pillars

1. Research & Development: Address global public health needs with a focus on clinical and pharmaceutical development

2. Public health-oriented portfolio & partnerships: Via public and private actors & networks, and through in-kind and direct contributions, build a public health oriented portfolio to deliver new and accessible treatments.

3. Sustainable access: Advocate for, facilitate and/or implement work related to Licensing, Public Health Policy & Use, Regulatory approvals in high-burden countries, Manufacturing & Supply, Procurement and Reimbursement models.

€500 million to accelerate development and delivery of 5 new treatments that address the most urgent public health needs
GARDP programme objectives

SERIOUS BACTERIAL INFECTIONS (SBI)

CHILDREN

Neonatal sepsis

Paediatrics

SEXUALLY TRANSMITTED INFECTIONS (STIs)

EXPLORATORY & DISCOVERY

• Accelerate development of new antibiotics to deliver at least one new treatment addressing serious infections in hospitalised adults caused by WHO priority pathogens

• Develop an alternative first-line treatment for clinically diagnosed cases of sepsis and a new treatment for confirmed multidrug resistant pathogens

• Repurpose and optimize use of old antibiotics and accelerate development of new antibiotics for at least one new and improved treatment for children

• Accelerate development of new antibiotics and develop at least one new treatment for difficult to treat and drug resistant infections

• Assess new antibiotics, ‘recovered’ drugs and combinations for inclusion in GARDP priority programs

• Identify novel antibiotics for new and under-exploited targets to translate into treatments for drug-resistant infections
GARDP pipeline

**RECOVERY EXPLORATORY/ DISCOVERY**

- NEONATAL SEPSIS
  - PK/PD studies
  - Fosfomycin Sandoz/Infectopharm
  - Flomoxef Shionogi

- PAEDIATRIC
  - Polymyxin B
  - Potential Asset: A
  - Broad CRE coverage
  - Potential Asset: B
  - CRAB coverage
  - Zoliflodacin Entasis-Therapeutics
  - Approved in Asia: CARB (CUTIS)

- STIs
  - Sitaflloxacin Daiichi-Sankyo
  - Potential Asset: C
  - Potential Asset: D
  - Active vs GC, CT and MG

- SERIOUS G-NEG BACTERIAL INFECTIONS
  - HIPS library screening
  - CALIBRE RefFRAME library screening
  - Japanese Consortium library screening (Eisai & Takeda)

**TRANSLATIONAL**

- Pre-clinical

**DEVELOPMENT**

- Phase I

- Phase II a PoC

- Phase IIb/III

- Registration
  - FDA approved; limited Paediatric label (no EU)
  - Approved in EU limited Neon/Peds label
  - Approved in Asia: Neo & Paeds data
  - TPP1 empiric combination Tx

**IMPLEMENTATION**

- Access-Stewardship
  - Strategy for WHO pre-qualification
  - Working on cost of goods reduction and access strategies
  - Considering Ph3 for adult SBIs (other than CUTIS)

**Material Transfer Agreement discussions**

**Term-sheet discussions**
GARDP Access framework for public health impact

<table>
<thead>
<tr>
<th>Licensing</th>
<th>Regulatory</th>
<th>Public Health Policy &amp; Use</th>
<th>Outsourcing Strategies</th>
<th>Procurement</th>
<th>Reimbursement Models</th>
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<tbody>
<tr>
<td>In &amp; out-licensing supporting:</td>
<td>Collaborating with WHO &amp; national regulators for:</td>
<td>Early Access programmes</td>
<td>Cost of goods focus</td>
<td>Better understanding national needs in key high-burden countries</td>
<td>Non-volume based sustainable reimbursement models</td>
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<td>Quality manufacturing</td>
<td>Public health evidence (need and use)</td>
<td>Guidelines to ensure appropriate access</td>
<td>Defining best practice in manufacturing</td>
<td>Maintaining a core network of partners</td>
<td>Facilitating cost-saving procurement mechanisms to support demand</td>
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<td>Early access across high-burden countries</td>
<td>Global registration</td>
<td>Surveillance for resistance emergence</td>
<td>Diagnostics for stewardship</td>
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<td>Appropriate marketing</td>
<td>Label extension</td>
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GARDP’s intensity of engagement will vary for each of these interventions and will include:

- Advocating
- Facilitating
- Implementing
**Short-term Target Product Profile for uncomplicated GC**

<table>
<thead>
<tr>
<th>Table Title</th>
<th>IDEAL</th>
<th>MINIMUM</th>
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</thead>
</table>
| **Activity against co-infecting STI pathogens** | *Chlamydia trachomatis*  
*Mycoplasma genitalium* | *Chlamydia trachomatis* |
| **Patient population** | Adults and adolescents | Adults and adolescents |
| **Clinical efficacy (Urogenital infections)** | 97% (95% CI, 95-100) | 95% (95% CI, 90-100) |
| **Clinical efficacy (Extra-genital infections)** | Equivalent to current treatment regimens | Equivalent to current treatment regimens |
| **Mechanism of action** | Bactericidal  
Intracellular activity | Bactericidal  
- |
| **Activity against resistant strains** | Activity against ESC and macrolide-resistant NG strains  
No cross resistance with other Ab | Activity against ESC and macrolide-resistant NG strains  
Limited cross-resistance with other Ab |
| **Safety and tolerability** | Safe in pregnancy and lactation  
No patient monitoring required | -  
Minimal outpatient monitoring required |
| **Contra-indications** | None | Pregnancy and lactation |
| **Drug-Drug Interaction profile** | None | Minimal |
| **Route of Administration / formulation** | Oral | Oral |
| **Dosing Schedule** | Single dose | Single dose |
| **Treatment duration** | One day | One day |
| **Stability** | Heat stable, 3-year shelf-life in region 4b | Heat stable, 2-year shelf-life in CRT |
| **Time to patient availability** | 5 years | 7 years |
# Long term Target Product Profile for uncomplicated GC

<table>
<thead>
<tr>
<th>Indication</th>
<th>IDEAL</th>
<th>MINIMUM</th>
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<tr>
<td>Uncomplicated and complicated GC</td>
<td>Uncomplicated GC</td>
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</table>
| Activity against co-infecting STI pathogens | *Chlamydia trachomatis*  
*Mycoplasma genitalium* | *Chlamydia trachomatis* |
| Patient population | Adults, children and adolescents | Adults, children and adolescents |
| Clinical efficacy (Urogenital infections) | 97% (95% CI, 95-100) | 95% (95% CI, 90-100) |
| Clinical efficacy (Extra-genital infections) | 97% (95% CI, 95-100) | 95% (95% CI, 90-100) |
| Mechanism of action | Unique mechanism | Bactericidal |
| Intracellular activity | Bactericidal | - |
| Activity against resistant strains | Activity against ESC and macrolide-resistant NG strains | Activity against ESC and macrolide-resistant NG strains |
| No cross resistance with other Ab | Limited cross-resistance with other Ab |
| Safety and tolerability | Safe in pregnancy and lactation | - |
| No patient monitoring required | Minimal outpatient monitoring required |
| Contra-indications | None | Pregnancy and lactation |
| Drug-Drug Interaction profile | None | Minimal |
| Route of Administration / formulation | Oral Fixed Dose Combination | Co-packaged loose oral combination |
| Dosing Schedule | Single dose | Multiple dose |
| Treatment duration | Up to 3 days | Up to 5 days |
| Stability | Heat stable, 3-year shelf-life in region 4b | Heat stable, 2-year shelf-life in CRT |
| Time to patient availability | 7 years | 10 years |
Zoliflodacin project

Mechanism of action
First-in-class drug (spiropyrimidinetrione)
Inhibits DNA biosynthesis by binding to topo II
Mode of Action (MoA) differs from other topo II inhibitors

Indication: Uncomplicated gonorrhea
Formulation: granules for oral suspension in shachet
Predicted dosage: 3 g single dose

Project aim: Register, launch and roll out zoliflodacin in a selected number of high-burden countries
Objectives
1) To ensure the registration of zoliflodacin by delivering pivotal clinical trial(s)
2) To generate the necessary evidence to support the integration of zoliflodacin into clinical and public health guidelines;
3) To ensure sustainable and equitable access to zoliflodacin by embedding access elements in the clinical development program;
4) To support pharmaceutical development of a robust and affordable commercial product

Industrial partner
Entasis Therapeutics Inc
Zoliflodacin development history

SAD: Single Ascending Dose
ADME: Absorption, Distribution, Metabolism and Excretion
FE: Food Effect
PK: Pharmacokinetics
BE: Bio-equivalence

- AZ-sponsored
  - SAD trial: n=66
  - ADME trial: n=6
  - Phase II trial: n=144
  - PK trial: n=8
  - TQT trial: n=72

- NIAID-sponsored
  - Phase II trial: n=144

- GARDP-sponsored
  - Phase III trial: n=928
  - FE trial: n=48
  - BE trial: n=928

- Powder for oral suspension
- Granules for oral suspension

# Project partners

<table>
<thead>
<tr>
<th>Institution</th>
<th>Country</th>
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<tr>
<td>Department of Reproductive Health and Research, World Health Organisation</td>
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<tr>
<td>(WHO)</td>
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<tr>
<td>Drugs for Neglected Disease <em>initiative</em> (DNDi)</td>
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<tr>
<td>Foundation for Innovative Diagnostics (FIND)</td>
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<tr>
<td>Entasis Therapeutics</td>
<td>USA</td>
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<tr>
<td>National Institute of Allergy and Infectious Diseases (NIAID)</td>
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<tr>
<td>University of Birmingham (UAB), Alabama</td>
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<tr>
<td>ICON GPHS</td>
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<td>Bell Flower Clinic, Indianapolis</td>
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<tr>
<td>Harborview Medical Center, Seattle</td>
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<td>Louisiana State University, New Orleans</td>
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<tr>
<td>MetroHealth Medical Center, Cleveland</td>
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<tr>
<td>San Francisco City Clinic, San Francisco</td>
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<tr>
<td>University of Florida</td>
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<tr>
<td>Centre for HIV &amp; STIs, National Institute for Communicable Diseases (NICD)</td>
<td>South Africa</td>
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<tr>
<td>Wits RHI, University of Witwatersrand</td>
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<tr>
<td>University of KwaZulu Natal (UKZN)</td>
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<tr>
<td>South Africa Medical Research Council (SA-MRC)</td>
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<tr>
<td>Bureau of AIDS, TB, and STIs, Department of Disease Control, Thai Ministry</td>
<td>Thailand</td>
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<td>of Public Health (MoPH)</td>
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<td>Thailand US CDC Collaboration (TUC)</td>
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<tr>
<td>Thai Red Cross AIDS Research Center (TRCARC)</td>
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<tr>
<td>University of Mahidol – Tropical Medicine Hospital</td>
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<tr>
<td>WHO Collaborating Center for STI, Orebro University Hospital</td>
<td>Sweden</td>
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<tr>
<td>Department of Infectious Diseases, Public Health Service Amsterdam</td>
<td>The Netherlands</td>
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Challenges in development new GC treatments

• Gap between regulatory requirements for uncomplicated gonorrhoea and the actual use of gonorrhoea drugs within the context of syndromic management
  o Comparator to be used in clinical development
  o Narrow non-inferiority margin
  o Differentiation of re-infections from microbiological failures
  o Activity against co-infecting pathogens
• Necessity to achieve high cure rates at pharyngeal sites
  o Single dose dogma
  o Lack of well-established *in vitro* and *in vivo* model for studying PK/PD
• Positioning of the drug (resistant infections vs clinical indication) and consequence for access and stewardship
• Clinical trials challenges
  o Inclusion of women and adolescents
  o Gathering of PK data from patients
  o Fragility of *Neisseria gonorrhoeae*
  o Differences in Standard of Care and Ethics/Regulatory requirements across countries
Thank you