



# Zoliflodacin: Addressing a growing global threat through a novel public-private development partnership

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October 18, 2024  
IDWeek 2024  
Los Angeles, CA

# Disclosures

- David Altarac MD is a full-time employee of Innoviva Specialty Therapeutics.
- All relevant financial disclosures have been mitigated.

# Gonorrhea is a growing global public health concern

Gonorrhea is the second most prevalent bacterial sexually transmitted infection<sup>1</sup>

CDC and WHO have raised alerts regarding ceftriaxone-resistant *Neisseria gonorrhoeae*<sup>2,3</sup>



U.S. Department of  
Health and Human Services  
Centers for Disease  
Control and Prevention



3

## RAPID COMMUNICATION

Extensively drug-resistant (XDR) *Neisseria gonorrhoeae* causing possible gonorrhoea treatment failure with ceftriaxone plus azithromycin in Austria, April 2022

4

## HEALTH

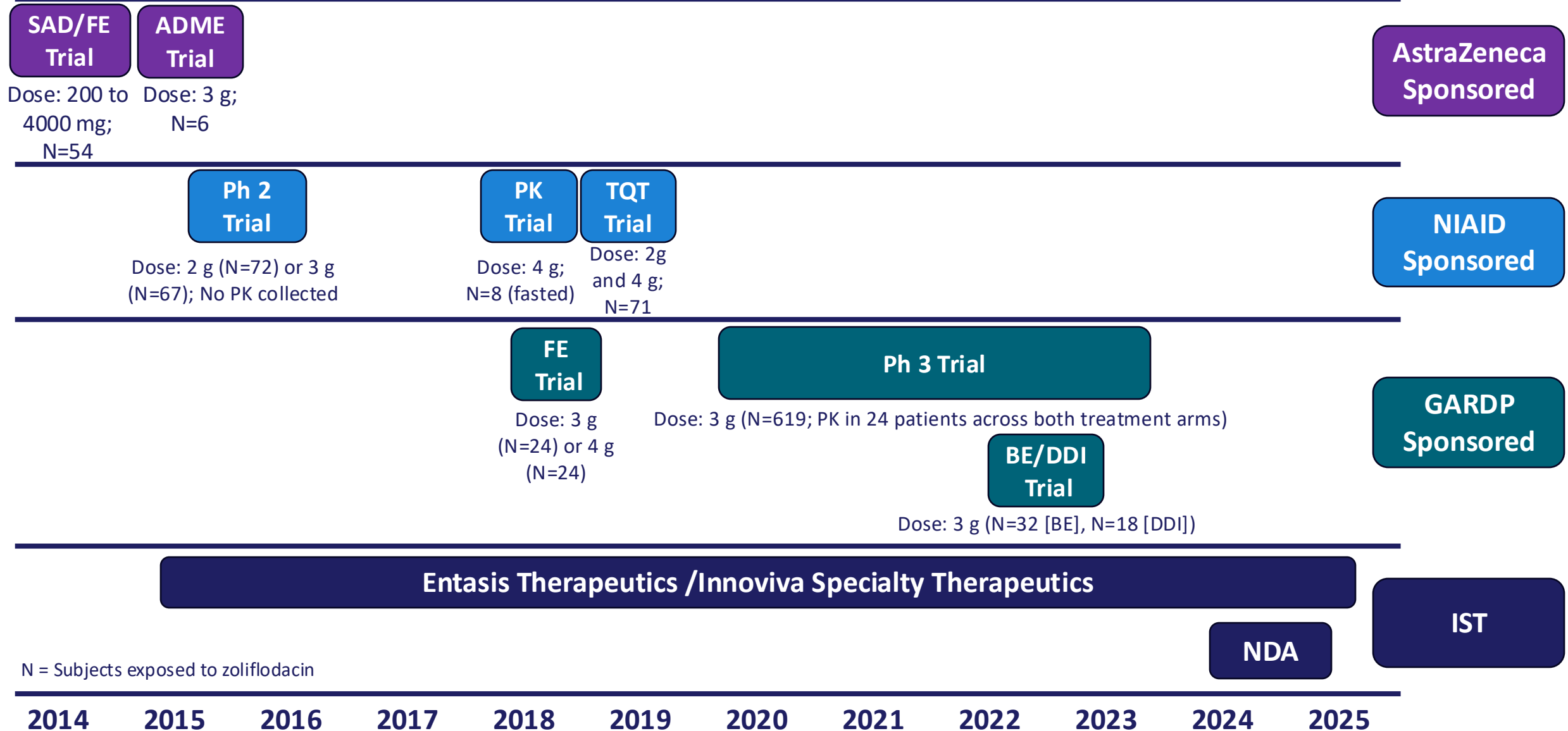
### New 'Superbug' Strain of Gonorrhea Is Outsmarting Most Antibiotics

Two cases in Massachusetts involve a novel strain more impervious to existing antibiotics than other strains in the U.S.

5

1. Workowski KA, et al. MMWR Recomm Rep. 2021 Jul 23;70(4):1-187.
2. World Health Organization. Gonorrhoea (*Neisseria gonorrhoeae* infection) Fact Sheet. [https://www.who.int/news-room/fact-sheets/detail/gonorrhoea-\(neisseria-gonorrhoeae-infection\)](https://www.who.int/news-room/fact-sheets/detail/gonorrhoea-(neisseria-gonorrhoeae-infection))
3. US Department of Health and Human Services and Centers for Disease Control and Prevention. Antibiotic Resistance Threats In The United States 2019. <https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf>
4. Pleininger S, et al. Euro Surveill. 2022;27(24):pii=2200455.
5. Mosbergen D. Wall Street Journal, January 29, 2023. <https://www.wsj.com/articles/new-superbug-strain-of-gonorrhea-is-outsmarting-most-antibiotics-11674947446>

# Zoliflodacin Development Through a Public-Private Partnership



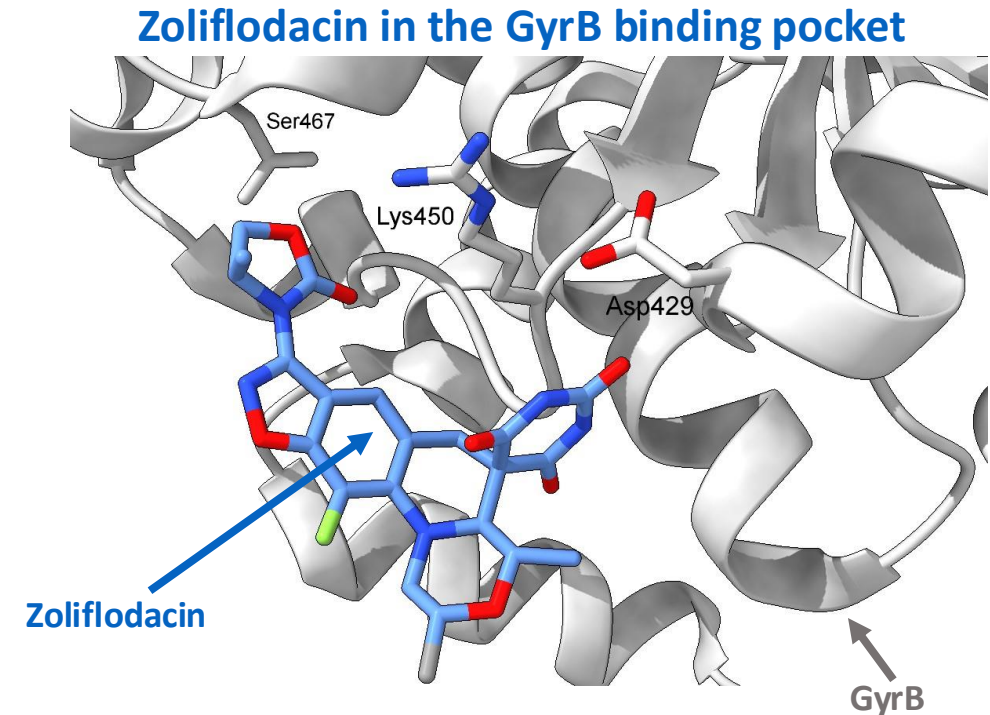
N = Subjects exposed to zoliflodacin

ADME, absorption, distribution, metabolism, elimination; BE, bioequivalence; DDI, drug-drug interaction; FE, food effect; PK, pharmacokinetics; TQ, thorough QT; SAD, single ascending dose  
SAD/FE trial: D4930C00001; ADME trial: D4930C00001; Phase 2 trial: NIAID 16-0014; PK trial: NIAID 16-0118; TQT trial: NIAID 16-0110;  
FE trial: GARDP-Z-0002 (STI\_Zoli002); Phase 3 trial: GARDP-Z-0001 (Zoli001); BE/DDI Trial: GARDP-Z-0003 (Zoli 003)

# Zoliflodacin For Treatment of Uncomplicated Gonorrhea

**Zoliflodacin is a first-in-class, single-dose, oral spiropyrimidinetrione antibiotic**

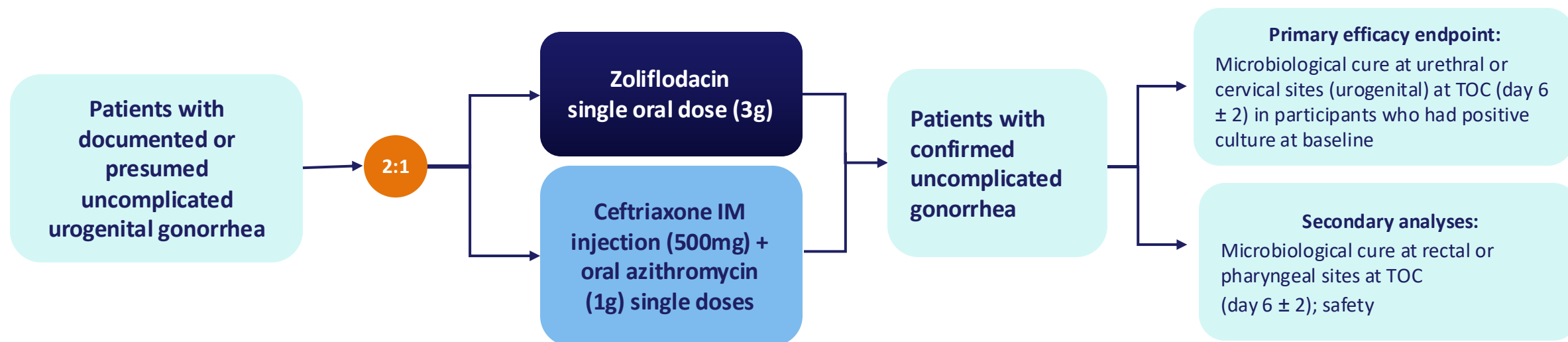
- Unique mode of inhibition resulting in no cross-resistance to other antibiotics including fluoroquinolones
- Bactericidal inhibition of DNA replication:
  - Primary target is GyrB subunit of DNA gyrase in a site distinct from fluoroquinolones which target the GyrA subunit
- In vitro activity against *Neisseria gonorrhoeae* including multidrug-resistant strains
  - low propensity to develop resistance in vitro



PDB ID 8BP2: Morgan H. *et al.* Int J Mol Sci. 2023, 24(2), 1634

# Pivotal Phase 3 Registrational, Randomized, Comparative Trial

Evaluate the safety and efficacy of zoliflodacin compared to combination of ceftriaxone + azithromycin



Trial designed with 90% power and a 12% noninferiority margin

- Phase 3 noninferiority trial analyzed a total of 930 patients with uncomplicated urogenital gonorrhea and included women (12%), adolescents (1.5%), and people living with HIV (21.4%)
- This is the largest trial conducted for a new gonorrhea treatment
- Global Phase 3 trial with recruitment from 18 clinical sites across 5 countries, including Belgium, the Netherlands, South Africa, Thailand, and the US

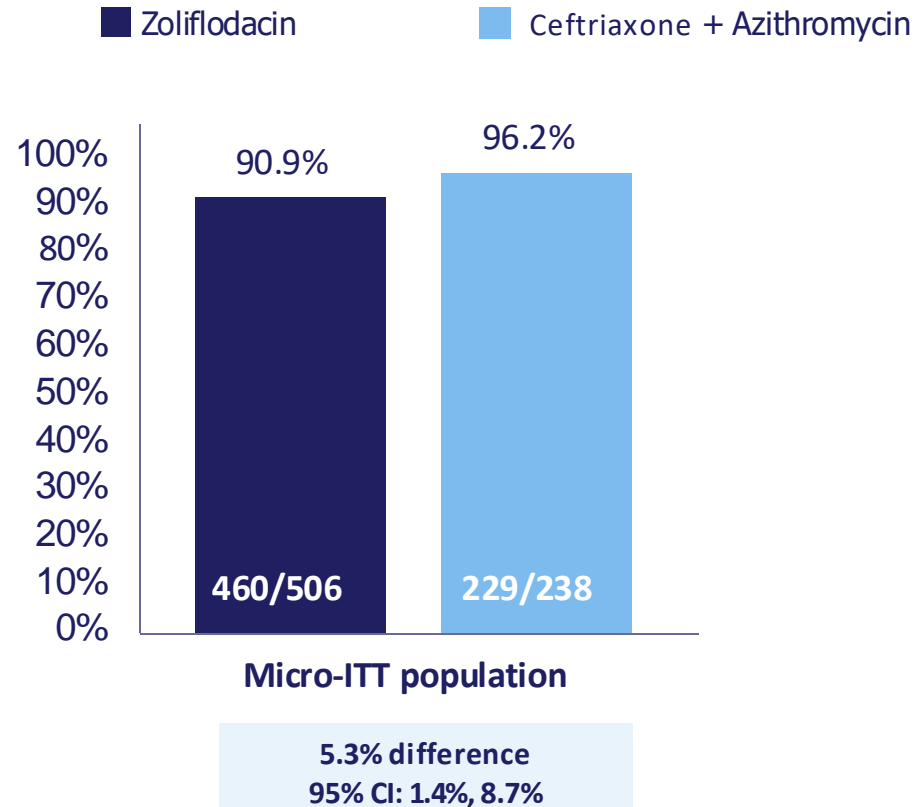
IM, intramuscular; TOC, test of cure

Luckey A, et al. Zoliflodacin is non-inferior to a combination of ceftriaxone and azithromycin for treatment of uncomplicated urogenital gonorrhoea: results of a large global Phase 3 trial. Oral Presentation OS246. Presented ECCMID 2024; Barcelona, Spain.

# Zoliflodacin Met The Primary Endpoint of Non-Inferiority

Microbiological cure was >90% at TOC in both treatment arms for patients with urogenital gonorrhea

## Microbiological cure rate at Test of Cure visit



Zoliflodacin met the primary efficacy endpoint of non-inferiority to the comparator at TOC visit in the urogenital Micro-ITT Population

- Treatment difference 5.3% (95% CI: 1.4%, 8.7%)
- Includes patients that did not comply with trial treatment, including those lost to follow-up
- In the evaluable population, the microbiological cure rate was 96.8% (460/475) for the zoliflodacin arm compared to 100% (229/229) for the comparator arm representing a difference of 3.16% (95% CI: 1.10 - 5.14).
  - The evaluable population included all randomized participants who had a positive *N. gonorrhoeae* culture at baseline and whose baseline AST result showed no pre-existing resistance to comparators, who did not vomit within 30 minutes of administration of drugs, and who had a *N. gonorrhoeae* culture result at the TOC visit.

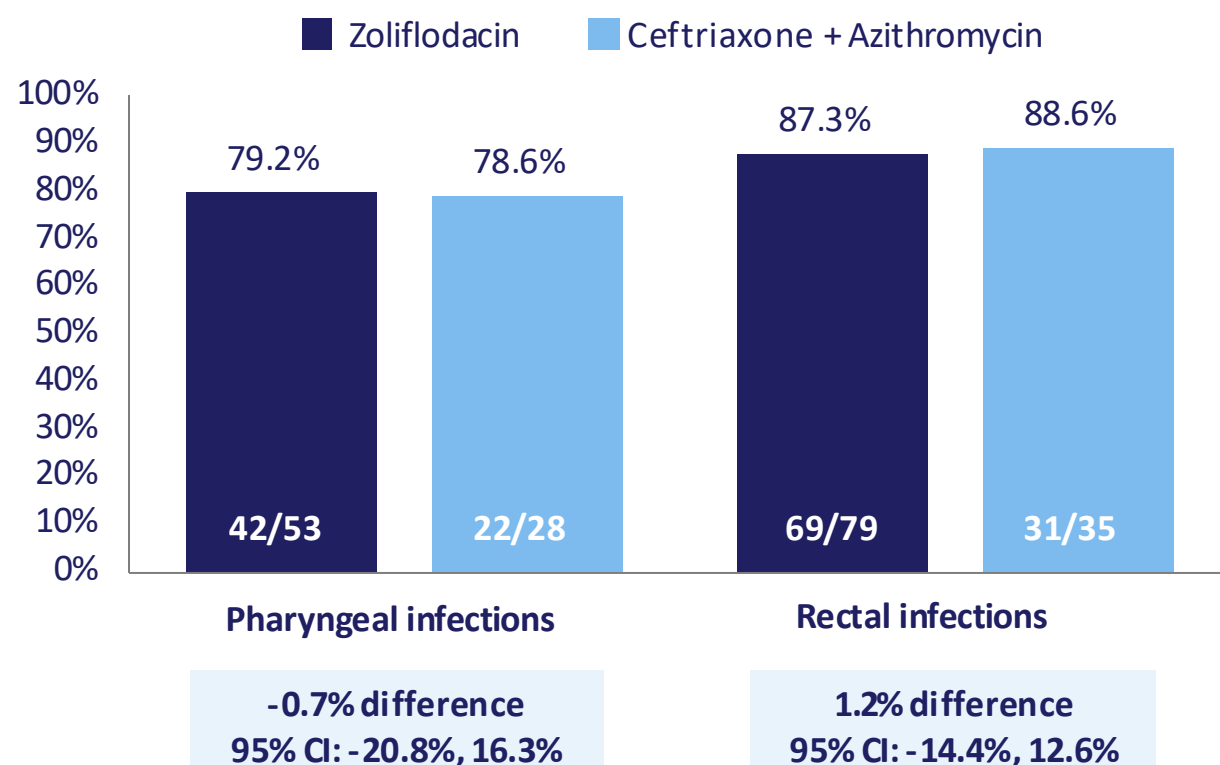
AST, antimicrobial susceptibility testing ; CI, confidence interval; Micro-ITT, microbiological intent-to-treat; TOC, test of cure

Luckey A, et al. Zoliflodacin is non-inferior to a combination of ceftriaxone and azithromycin for treatment of uncomplicated urogenital gonorrhoea: results of a large global Phase 3 trial. Oral Presentation OS246. Presented ECCMID 2024; Barcelona, Spain.

# Microbiological Cure in Pharyngeal and Rectal Gonorrhea

Key secondary analyses were comparable between treatment arms

## Microbiological cure rate at TOC visit (Micro-ITT population)



- Key secondary analysis included participants with pharyngeal and rectal gonorrhea
  - Historically lower rates of cure than those observed in urogenital disease
- Rates of cure in the zoliflodacin arm were comparable to those observed in the comparator arm
- These secondary analyses were not powered for statistical significance

AST, antimicrobial susceptibility testing ; CI, confidence interval; Micro-ITT, microbiological intent-to-treat; TOC, test of cure

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# Overall Summary of Adverse Reactions

Adverse reactions $\geq$ 1% in either arm	ZOLI N = 619 %	CRO + AZM N = 308 %
Headache	7.6	1.9
Dizziness	2.7	0.6
Nausea	2.1	3.6
Diarrhea	1.3	6.8
Abdominal pain <sup>1</sup>	1.2	0.3
Neutropenia	0.8	1.6
Injection site pain	0.0	12.3

No emergence of zoliflodacin resistance following therapy was detected

CRO + AZM, ceftriaxone and azithromycin

<sup>1</sup>Includes the preferred terms abdominal pain, abdominal pain upper and abdominal pain lower

# Conclusions

**Public, private partnerships are helping to address the many challenges in antibiotic drug development**

**In a Phase 3 trial, zoliflodacin met the primary efficacy endpoint of noninferiority to ceftriaxone + azithromycin for microbiological cure in patients with uncomplicated urogenital infections due to *N. gonorrhoeae***

- Zoliflodacin vs ceftriaxone + azithromycin microbiological cure rates were 90.9% vs 96.2%, respectively, at urogenital site (Micro-ITT population)

**Zoliflodacin was well tolerated and had a comparable safety profile to ceftriaxone + azithromycin**

**If approved, zoliflodacin could be an important treatment option for uncomplicated gonorrhea infections**

- Single oral dose
- Demonstrates in vitro activity against multidrug-resistant strains

# Acknowledgements

- Global investigators, sites and study participants
- GARDP Team
- Innoviva Specialty Therapeutics team, including past and present Entasis Therapeutics and AstraZeneca team members
- NIAID Team
- Additional Presentations at IDWEEK: Friday, October 18, 2024, Hall J & K
  - Poster P-1251 - Pharmacometric Analyses to Support Dose Selection of Zoliflodacin, a First-in-Class Oral Antibiotic Being Developed for the Treatment of Uncomplicated Gonorrhea
  - Poster P-1103 - In Vitro Activity of Zoliflodacin against Baseline *Neisseria gonorrhoeae* Isolates from US Participants in a Global Phase 3 Randomized Controlled Trial

The STI\_Zoli001 trial was funded with support from the governments of Germany (BMBF and BMG), UK (GAMRIF, part of DHSC, and DFID), Japan (MHLW), the Netherlands (Ministries of VWS and BZ), Switzerland (FOPH), The Grand Duchy of Luxembourg, as well as the Canton of Geneva, the South African Medical Research Council (SAMRC), and the Leo Model Foundation. The views expressed in this presentation are those of the authors and not necessarily those of the funding bodies.