Oral zoliflodacin is non-inferior to a combination of ceftriaxone and azithromycin for treatment of uncomplicated urogenital gonorrhoea: Results of a large global Phase 3 randomised controlled trial

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on behalf of the Zoliflodacin Phase 3 Trial Group

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GARDP INNOVIVA Specialty Therapeutics

Conflicts of interest disclosure

- H.J.C. de Vries: none reported.
- Zoliflodacin is co-developed by GARDP in collaboration with Entasis Therapeutics, Inc., an affiliate of Innoviva Specialty Therapeutics, Inc., and a subsidiary of Innoviva, Inc. (Nasdaq: INVA).

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- The views expressed in this presentation are those of the authors and not necessarily those of the funding bodies.

Gonorrhoea

RAPID COMMUNICATION

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

- Major global Public Health concern
  - WHO estimate 82.4 million new cases among adolescents and adults aged 15–49 years worldwide
  - Highest burden of disease in WHO African and Western Pacific regions
  - WHO goal to reduce global STI burden by 90% by 2030

- Increasing multi-drug resistance
  - Emerging resistance/reduced susceptibility to extended spectrum cephalosporins
  - WHO priority pathogen in urgent need of new treatments
  - Surveillance data on antibiotic resistance and treatment failures from LMIC are scarce

- Current treatment recommendations
  - Syndromic management
  - Single therapy: ceftriaxone IM 250 mg to 1 g
  - Dual therapy: ceftriaxone IM 250 mg to 1 g and oral azithromycin 1 g
  - New treatments in late clinical development: zoliflodacin and gepotidacin


HEALTH

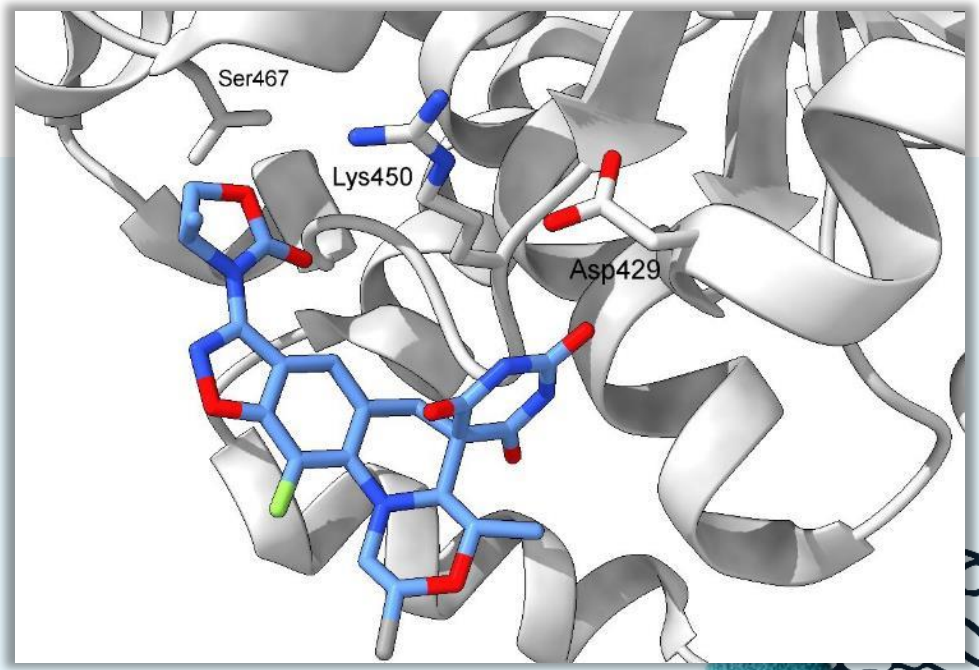
New 'Superbug' Strain of Gonorrhea Is Outsmarting Most Antibiotics

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

References: Unemo M et al. Lancet Microbe. 2021; 2(11):e627-e636.
Guidelines for the management of symptomatic sexually transmitted infections. Geneva: WHO; 2021.
Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Geneva: WHO; 2021.
Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: WHO; 2017.

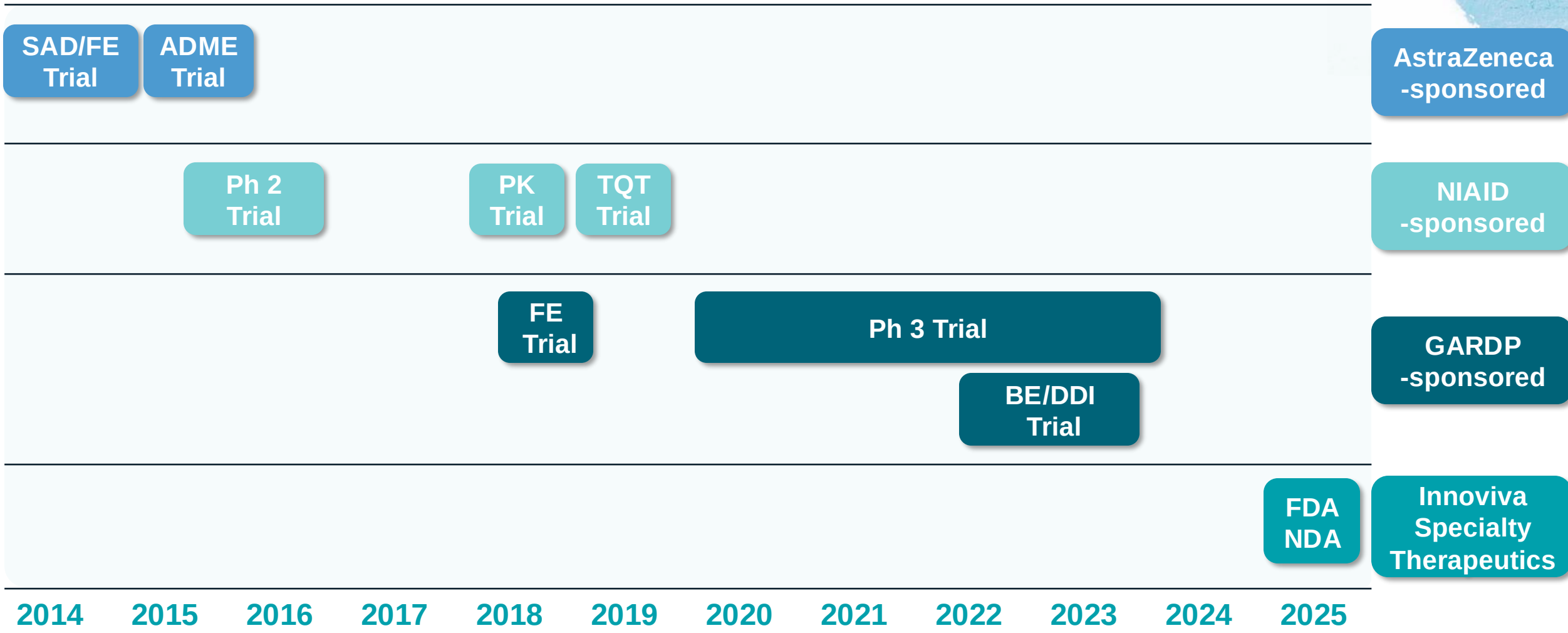
Zoliflodacin: investigational oral treatment for uncomplicated gonorrhoea

- **First-in-class antibiotic**
  with distinct mode of action through interaction with topoisomerase II complex (GyrB)
- **Microbiological potency**
  against *Neisseria gonorrhoeae* (MIC_{90} of 0.12 mg/L) including multi-drug resistant strains
- **Low propensity**
  to development of *in vitro* resistance
- **Single oral dose**
  for the proposed indication of uncomplicated gonorrhoea



References: Bradford PA, *et al*., ACS Infectious Diseases 2020; 6(6);1332-1345
Diagram derived from Morgan H, *et al*., Int. J. Mol. Sci. 2023; 24(2); 1634

Zoliflodacin development through a novel public-private partnership

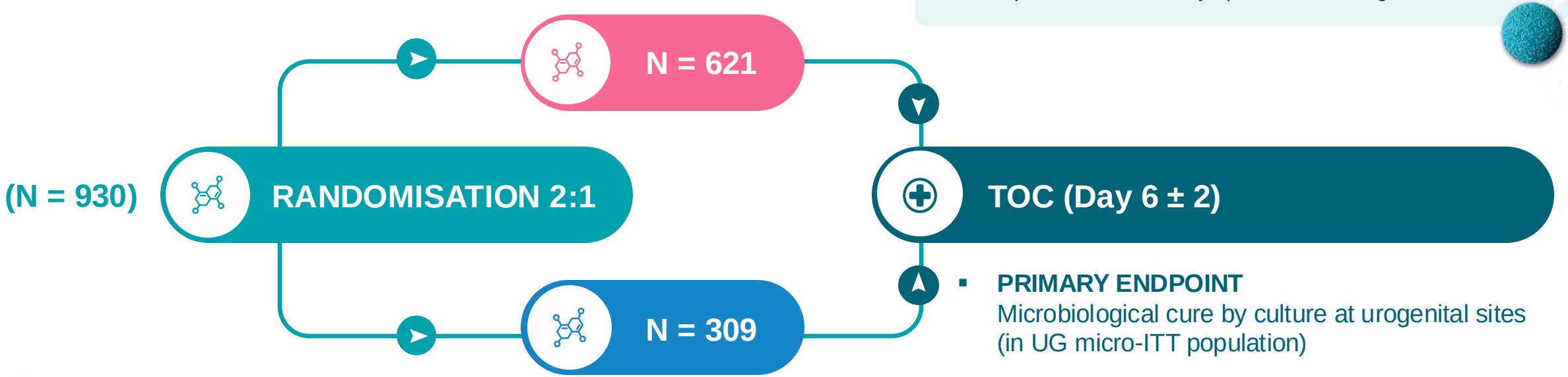


Abbreviations: ADME, absorption, distribution, metabolism, excretion; BE, bioequivalence; DDI, drug-drug interaction; FE, food effect; GARDP: Global Antibiotic R&D Partnership; N: number of participants exposed to zoliflodacin; NDA: new drug application; NIAID: National Institute of Allergy and Infectious Diseases (NIH, USA); PK: pharmacokinetics; TQT: thorough QT; SAD, single ascending dose.

GARDP-sponsored zoliflodacin Phase 3 registration trial design

KEY INCLUSION CRITERIA

- Age ≥ 12 years
- Signs and symptoms of uncomplicated urethral or endocervical gonorrhoea **and/or**
- Culture, Gram stain or NAAT positive for NG within 14 days prior to screening **and/or**
- Unprotected sexual contact with confirmed infected partner within 14 days prior to screening

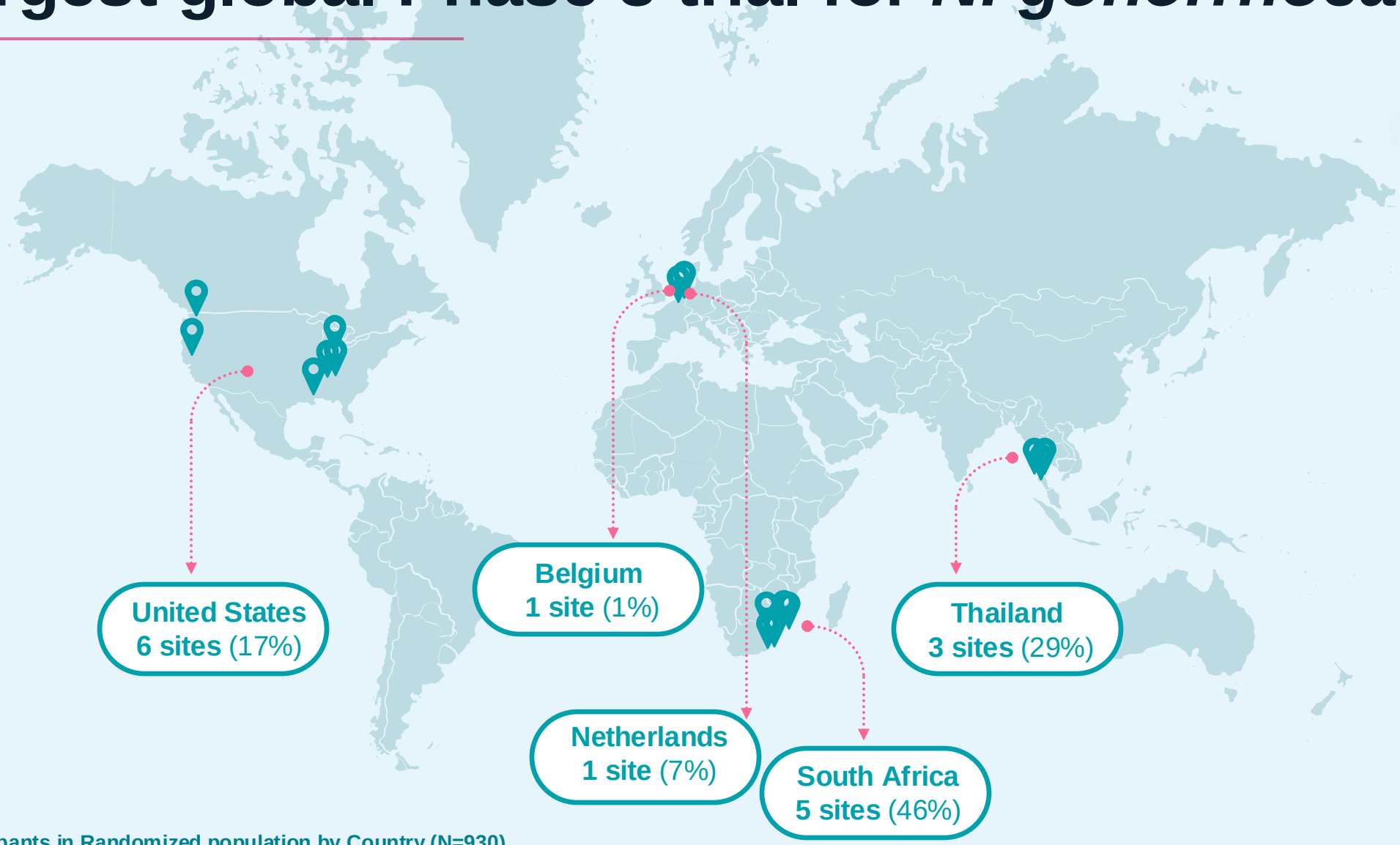


- Zoliflodacin (single dose, 3 g, granules for oral suspension)
- Ceftriaxone (single dose, 500 mg, IM), plus
- Azithromycin (single dose, 1 g, oral)

- **PRIMARY ENDPOINT**
  Microbiological cure by culture at urogenital sites (in UG micro-ITT population)
- **NON-INFERIORITY MARGIN 12%**

Abbreviations: IM = intramuscular; micro-ITT = microbiological ITT; NAAT: nucleic acid amplification test; N = number of participants; NG = *Neisseria gonorrhoeae*; TOC = test of cure; UG = urogenital (urethral or cervical).

Largest global Phase 3 trial for *N. gonorrhoeae*



% of participants in Randomized population by Country (N=930)

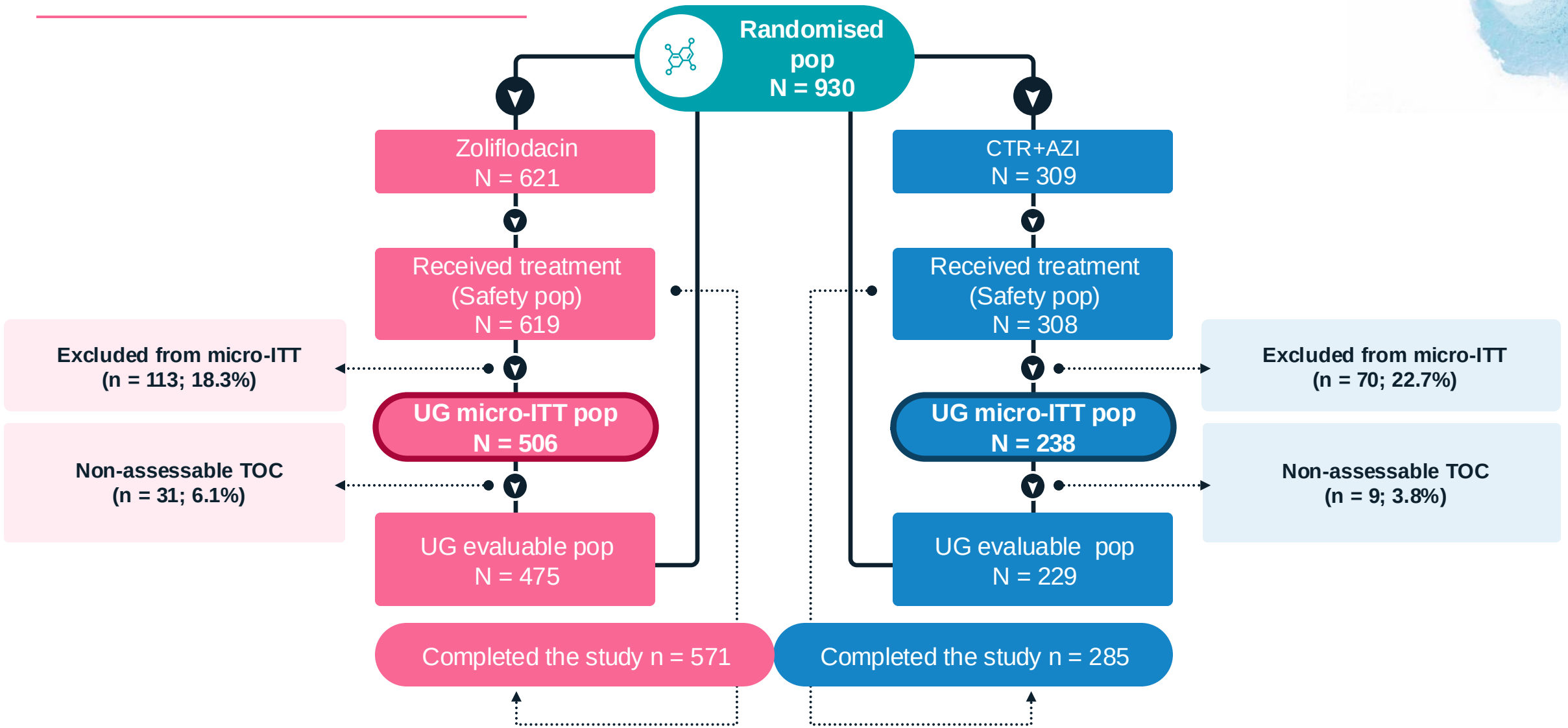
Summary baseline participant characteristics

Results presented at *ESCMID Global, April 27-30 2024, Barcelona, Spain (Abstract 01099).*

PARAMETER	Zoliflodacin (N = 621)	CTR+AZI (N = 309)	Overall (N = 930)
AGE [years]			
Mean (SD) [Min – Max]	30.0 (9.56) [16 – 73]	29.2 (9.13) [15 – 67]	29.7 (9.42) [15 – 73]
≥ 18 years	609 (98.1)	307 (99.4)	916 (98.5)
SEX AT BIRTH [n (%)]			
Male	544 (87.6)	271 (87.7)	815 (87.6)
RACE* [n (%)]			
White	66 (10.6)	47 (15.2)	113 (12.2)
Black/African American	349 (56.2)	165 (53.4)	514 (55.3)
American Indian or Alaska Native	8 (1.3)	1 (0.3)	9 (1.0)
Native Hawaiian or Other Pacific Islander	2 (0.3)	1 (0.3)	3 (0.3)
Asian	193 (31.1)	92 (29.8)	285 (30.6)
White, Asian	1 (0.2)	2 (0.6)	3 (0.3)
Other	2 (0.3)	1 (0.3)	3 (0.3)
HIV STATUS [n (%)]			
Positive	134 (21.6)	65 (21.0)	199 (21.4)

Abbreviations: CTR+AZI = ceftriaxone+azithromycin; N= number of participants in Randomised Population; n = number of participants; SD = standard deviation.
Percentages calculated as n/N x 100.
*FDA categorisation

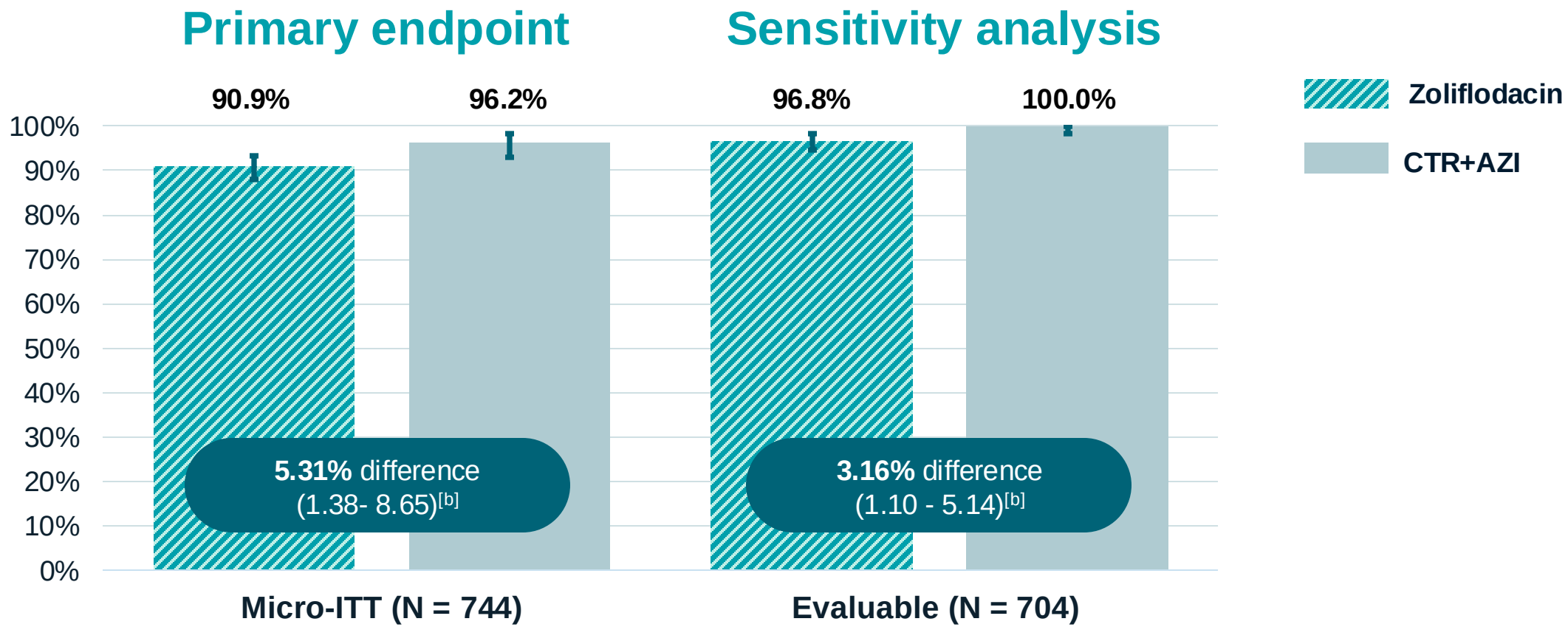
Participant disposition



Abbreviations: CTR+AZI = ceftriaxone+azithromycin; micro-ITT = microbiological ITT; N = number of participants in specified population; n = number of participants; TOC = test of cure; UG = urogenital (urethral or cervical).

Zoliflodacin was non-inferior to the comparator*

UROGENITAL MICROBIOLOGICAL CURE RATE (95%CI)[a] AT TOC VISIT

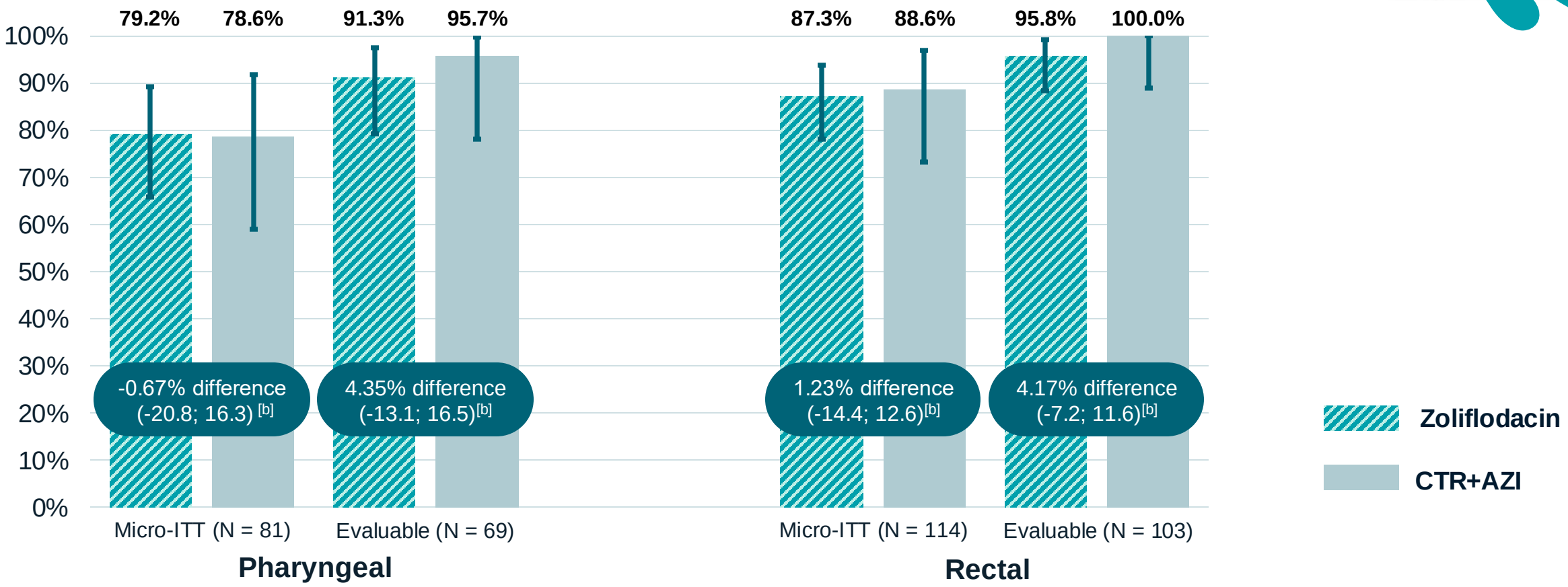


Abbreviations: CI = confidence interval; CTR+AZI = ceftriaxone+azithromycin; micro-ITT = microbiological ITT; N = number of participants in the micro-ITT/Evaluable Population for the specified body site; TOC = test of cure; UG = urogenital.
The percentages are calculated as 100 x (n/N).
[a] Calculated with the Clopper-Pearson method.
[b] Calculated with the Newcombe score method.

***Reference:** A Luckey, H Broadhurst, P Daram, S Delany-Moretlwe, HJC de Vries, R Kittiyaowamarn, D Lewis, JP Mueller, S O'Brien, MA Richardson, S Srinivasan, SN Taylor, M Unemo, E Hook III, for the zoliflodacin Phase 3 study group. Abstract number 01099; ESCMID Global, April 27-30 2024, Barcelona, Spain.

Microbiological efficacy at extragenital sites

MICROBIOLOGICAL CURE RATE (95%CI)[a] AT TOC VISIT



Abbreviations: CI = confidence interval; CTR+AZI = ceftriaxone+azithromycin; micro-ITT = microbiological ITT; N: number of participants in micro-ITT/Evaluable population for the specified body site; TOC = test of cure.
The percentages are calculated as 100 x (n/N).
[a] Calculated with the Clopper-Pearson method.
[b] Calculated with the Newcombe score method.

Zoliflodacin has a similar adverse event profile to comparator

	Zoliflodacin (N = 619) n (%)	CTR+AZI (N = 308) n (%)	Overall (N = 927) n (%)
All AEs	287 (46.4)	144 (46.8)	431 (46.5)
Related AEs	117 (18.9)	76 (24.7)	193 (20.8)
Serious AEs	0	0	0
Related serious AEs	0	0	0
AEs leading to treatment discontinuation	0	0	0
AEs leading to death	0	0	0
AEs by maximum severity[a]			
▪ Grade 1 – Mild	157 (25.4)	82 (26.6)	239 (25.8)
▪ Grade 2 – Moderate	109 (17.6)	44 (14.3)	153 (16.5)
▪ Grade 3 – Severe	20 (3.2)	18 (5.8)	38 (4.1)
▪ Grade 4 – Life-Threatening	1 (0.2)	0	1 (0.1)
▪ Grade 5 – Death	0	0	0

Abbreviations: AE = Adverse event; CTR+AZI = ceftriaxone+azithromycin; n = number of participants with AEs; N = number of participants in the Safety population. The percentages are calculated on the number of participants per treatment arm = 100 x (n/N).
[a] Based on Common Terminology Criteria for Adverse Events (CTCAE).

***Reference:** Luckey, A. et al. Abstract number 01099; ESCMID Global 2024; oral presentation, April 27-30 2024, Barcelona, Spain.

Favourable safety and tolerability profile

TREATMENT EMERGENT ADVERSE EVENT BY PREFERRED TERM (≥3% Overall)	Zoliflodacin (N = 619) n (%)	CTR+AZI (N = 308) n (%)	Overall (N = 927) n (%)
Subjects with at least one TEAE	286 (46.2)	143 (46.4)	429 (46.3)
Headache	61 (9.9)	14 (4.5)	75 (8.1)
Neutropenia	42 (6.8)	24 (7.8)	66 (7.1)
Injection site pain	5 (0.8)	38 (12.3)	43 (4.6)
Diarrhoea	15 (2.4)	22 (7.1)	37 (4.0)
Neutrophil count decreased	21 (3.4)	15 (4.9)	36 (3.9)
Leukopenia	24 (3.9)	7 (2.3)	31 (3.3)
Nausea	16 (2.6)	12 (3.9)	28 (3.0)

Abbreviations: CTR+AZI = ceftriaxone+azithromycin; n = number of participants with TEAEs, N = number of participants in the Safety population; TEAE = treatment emergent adverse event. The percentages are calculated on the number of participants per treatment arm = 100 x (n/N).

Baseline isolates (N=936) antimicrobial susceptibility profile*

Antimicrobial	(µg/mL)			Resistant[a] (%)
	MIC_{50}	MIC_{90}	Range	EUCAST
Zoliflodacin	0.06	0.12	≤0.008 -0.5	NA
Ceftriaxone	0.004	0.015	≤0.002 - >0.5	0.4
Azithromycin	0.12	1	≤0.06 - >8	6.0
Cefixime	0.008	0.03	≤0.002 - >0.5	1.5
Ciprofloxacin	2	>2	≤0.0005 - >2	75.7
Gentamicin	8	8	≤0.5 - 16	NA
Spectinomycin	32	32	≤4 - 64	0
Tetracycline	>4	>4	≤0.12 - >4	74.3

- No major differences between the two treatment arms in primary population (UG) baseline isolates' MIC distribution
- No shift in zoliflodacin, azithromycin or ceftriaxone MIC distribution at test-of-cure

Abbreviations: CLSI: Clinical and Laboratory Standards Institute; EUCAST: European Committee on Antimicrobial Susceptibility Testing; N: number of isolates; MIC: minimum inhibitory concentration; Micro-ITT: microbiological intention to treat; MIC_{50}: MIC required to inhibit growth of 50% of isolates; MIC_{90}: MIC required to inhibit growth of 90% of isolates; NA: not applicable, UG: urogenital.
[a]MIC breakpoints obtained from: EUCAST 'Breakpoint tables for interpretation of MICs and zone diameters, version v12.0'.

***Reference:** A Luckey, V Elango, E Bettiol, LJV Piddock, M Unemo, P Bradford, S M McLeod, JP Mueller, S Srinivasan for the zoliflodacin Phase 3 study group. Poster P2527; ESCMID Global, April 27-30 2024, Barcelona, Spain.

Summary

1. This is a large, well conducted, global pivotal Phase 3 trial
2. Non-inferiority of zoliflodacin microbiological cure rate at TOC at urogenital site has been demonstrated
3. High microbiological cure rates are observed at urogenital and extragenital sites of infection
4. A single oral 3 g dose of zoliflodacin is generally well tolerated with a comparable safety profile to the standard of care
5. Favourable benefit/risk supports progression to new drug application (NDA) submission to FDA

Acknowledgments – Zoliflodacin Phase 3 Study Group

All Trial Participants

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Wits RHI, Johannesburg	▪ Prof Sinead Delany-Moretlwe ▪ Mbali Zulu	
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- Advisors:
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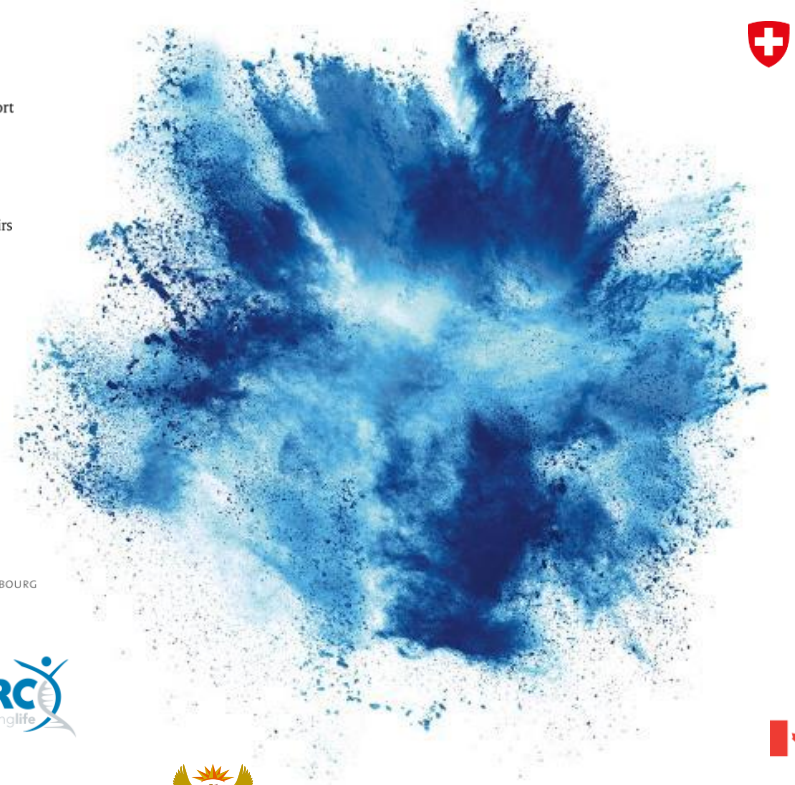
  - Angèle Gayet-Ageron, Geneva University Hospitals
  - Teodora Wi, WHO
- Current and former GARDP and IST collaborators and consultants



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Back-up

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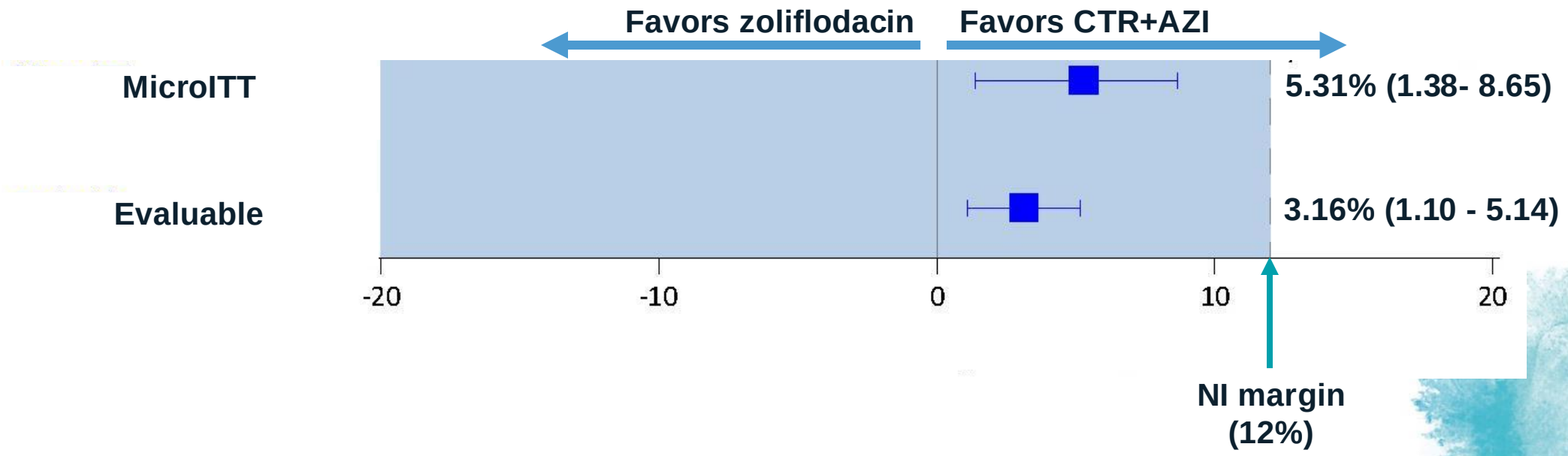
Zoliflodacin was non-inferior to the comparator

Primary endpoint achieved

Difference in microbiological cure rate at TOC at UG site, % (CI)[a]



Abbreviations: CI = confidence interval; CTR+AZI = ceftriaxone+azithromycin; micro-ITT = microbiological ITT; TOC = test of cure; UG = urogenital.
The percentages are calculated as 100 x (n/N).
[a] Calculated with the Newcombe score method.

Baseline urogenital isolates susceptibility profile

No major differences in MIC distribution between the two treatment arms in primary population (UG)

	Baseline isolates from urogenital micro-ITT population				
Treatment group (UG)	**Antimicrobial**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**	**Range (mg/L)**	**Resistant [a] (%)**
Zoliflodacin arm (N = 505)	Azithromycin	0.12	1	≤0.06, >8	5.7
	Cefixime	0.008	0.06	≤0.002, >0.5	1.2
	Ceftriaxone	0.004	0.015	≤0.002, 0.25	0.2
	Ciprofloxacin	2	>2	≤0.0005, >2	74.9
	Gentamicin	8	8	1, 16	NA
	Spectinomycin	32	32	8, 64	0
	Tetracycline	>4	>4	≤0.12, >4	71.5
	Zoliflodacin	0.06	0.12	≤0.008, 0.5	NA
CTR+AZI arm (N = 236)	Azithromycin	0.12	1	≤0.06, >8	5.1
	Cefixime	0.008	0.03	≤0.002, 0.5	1.3
	Ceftriaxone	0.008	0.015	≤0.002, 0.12	0%
	Ciprofloxacin	2	>2	0.002, >2	75.4
	Gentamicin	8	8	≤0.5, 16	NA
	Spectinomycin	32	32	8, 64	0
	Tetracycline	>4	>4	≤0.12, >4	75.4
	Zoliflodacin	0.06	0.12	≤0.008, 0.25	NA

Abbreviations: micro-ITT: microbiological intention to treat; CTR: ceftriaxone; AZI: azithromycin; NA: not applicable; UG: urogenital.
[a] EUCAST Breakpoint criteria for *N. gonorrhoeae* 'Breakpoint tables for interpretation of MICs and zone diameters', version v12.0

Test of cure urogenital isolates susceptibility profile

No shift in zoliflodacin, azithromycin or ceftriaxone MIC distribution at test of cure

	Test of cure isolates from urogenital micro-ITT population				
Treatment group (UG)	**Antimicrobial**	**MIC_{50} (mg/L)**	**MIC_{90} (mg/L)**	**Range (mg/L)**	**Resistant [a] (%)**
Zoliflodacin arm (N = 15)	Azithromycin	0.12	0.25	≤0.06, 2	6.7%
	Cefixime	0.008	0.015	≤0.002, 0.03	0%
	Ceftriaxone	0.008	0.015	≤0.002, 0.015	0%
	Ciprofloxacin	2	>2	0.004, >2	86.7%
	Gentamicin	8	8	4, 8	NA
	Spectinomycin	32	32	16, 32	0%
	Tetracycline	>4	>4	0.5, >4	66.7%
	Zoliflodacin	0.06	0.12	≤0.008, 0.25	NA
CTR+AZI arm (N = 0)	No isolates at test of cure in this treatment arm				

Abbreviations: micro-ITT: microbiological intention to treat; CTR: ceftriaxone; AZI: azithromycin; NA, not applicable; UG: urogenital.

[a]EUCAST Breakpoint criteria for *N. gonorrhoeae* 'Breakpoint tables for interpretation of MICs and zone diameters', version v12.0