Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Taylor SN, Marrazzo J, Batteiger BE, et al. Single-dose zoliflodacin (ETX0914) for treatment of urogenital gonorrhea. N Engl J Med 2018;379:1835-45. DOI: 10.1056/NEJMoa1706988

Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea

Supplemental Materials

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Table S1. Protocol Screening Exclusion Criteria

Additional Exclusion Criteria

1. Confirmed or suspected, complicated or systemic gonorrhea such as pelvic inflammatory disease, testicular pain, epididymitis, arthritis, conjunctivitis or endocarditis or clinical proctitis.
2. Known concomitant infection which would require immediate additional systemic antibiotics
3. Female subject currently breastfeeding
4. Use of systemic corticosteroid drugs or other immunosuppressive therapy within 30 days prior to enrollment
5. Cytotoxic chemotherapy or radiation therapy within the previous 3 months
6. Known chronic renal, hepatic (including chronic hepatitis B or hepatitis C infection) or hematologic impairment, or other condition that could interfere with the absorption or metabolism of study drug
7. Any concomitant condition that, in the opinion of the Investigator, would preclude an evaluation of a response or make it unlikely that the course of therapy and follow-up could be completed
8. A. Subject HIV-infected and taking antiretroviral medication
   B. Subject not HIV-infected and taking antiretroviral for pre- or post- exposure prophylaxis
   C. Subject newly diagnosed with HIV infection or known to be HIV-infected with evidence of immunosuppression, such as documented or patient reported CD4 count of < 200
9. Receipt or planned receipt of an investigational product in a clinical trial within 30 days prior to or 7 days after study dose administration
10. Female subject is not willing to defer treatment for bacterial vaginosis until Visit 2 if she tests positive for bacterial vaginosis at Visit 1
11. Use of drugs that act as inducer/inhibitors of CYP3A4/5 or the P-gp efflux transporter* within 30 days prior to study drug administration * such as itraconozale, fluconazole, ketoconazole, verapamil, diltiazem, amiodarone, felodipine, carbamazepine, phenytoin, or St. John's wort
12. Subjects with medically documented cardiac arrhythmia
13. Known allergy to lidocaine (or local anesthetics of the amide type, e.g., articaine, bupivacaine, mepivacaine, prilocaine, ropivacaine) or the antimicrobial preservative methylparaben.

30 **Table S2. Participants with AEs by MedDRA System Organ Class, Severity, Relationship and Therapy**

	Zoliflodacin 2000mg (N=72)					Zoliflodacin 3000mg (N=67)					Ceftriaxone 500mg (N=40)				
	Severity[1]			Relationship to Study Product[2]		Severity[1]			Relationship to Study Product[2]		Severity[1]			Relationship to Study Product[2]	
	Mild	Moderate	Severe	Not Related	Related	Mild	Moderate	Severe	Not Related	Related	Mild	Moderate	Severe	Not Related	Related
MedDRA System Organ Class	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any System Organ Class	14 (19)	4 (6)	0 (0)	9 (13)	9 (13)	20 (30)	3 (4)	1 (1)	12 (18)	12 (18)	14 (35)	4 (10)	0 (0)	12 (30)	6 (15)
Blood And Lymphatic System Disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal Disorders	5 (7)	0 (0)	0 (0)	1 (1)	4 (6)	8 (12)	0 (0)	0 (0)	1 (1)	7 (10)	3 (8)	0 (0)	0 (0)	1 (3)	2 (5)
General Disorders And Administration Site Conditions	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	1 (3)	1 (3)
Hepatobiliary Disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	1 (3)	0 (0)
Infections And Infestations	4 (6)	0 (0)	0 (0)	4 (6)	0 (0)	9 (13)	1 (1)	0 (0)	8 (12)	2 (3)	10 (25)	0 (0)	0 (0)	10 (25)	0 (0)
Injury, Poisoning And Procedural Complications	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Investigations	1 (1)	3 (4)	0 (0)	2 (3)	2 (3)	1 (1)	1 (1)	0 (0)	2 (3)	0 (0)	0 (0)	1 (3)	0 (0)	1 (3)	0 (0)
Metabolism And Nutrition Disorders	2 (3)	0 (0)	0 (0)	2 (3)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	1 (3)	0 (0)	1 (3)	0 (0)
Musculoskeletal And Connective Tissue Disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	1 (3)
Nervous System Disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (9)	0 (0)	0 (0)	1 (1)	5 (7)	2 (5)	0 (0)	0 (0)	1 (3)	1 (3)
Psychiatric Disorders	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

	Zoliflodacin 2000mg (N=72)					Zoliflodacin 3000mg (N=67)					Ceftriaxone 500mg (N=40)				
	Severity[1]			Relationship to Study Product[2]		Severity[1]			Relationship to Study Product[2]		Severity[1]			Relationship to Study Product[2]	
	Mild	Moderate	Severe	Not Related	Related	Mild	Moderate	Severe	Not Related	Related	Mild	Moderate	Severe	Not Related	Related
MedDRA System Organ Class	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Renal And Urinary Disorders	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Reproductive System And Breast Disorders	3 (4)	0 (0)	0 (0)	1 (1)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	1 (3)	1 (3)
Respiratory, Thoracic And Mediastinal Disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Skin And Subcutaneous Tissue Disorders	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Note: Denominator for percentages is the number of subjects in the population (N) for each therapy.
[1]For severity, a subject is only counted once per preferred term and is summarized according to their highest severity.
[2]For relationship, a subject is only counted once per preferred term and is summarized according to their closest relationship.

Table S3. *N. gonorrhoeae* Antimicrobial Susceptibility of Baseline Isolates According to Anatomic Site (Micro-ITT Population) All protocol antimicrobials

Specimen	Antimicrobial	MIC Breakpoint	MIC50 (µg/mL)	MIC90 (µg/mL)	Range (µg/mL)	Proportion at or above MIC Breakpoint n/N (%)
Urethral/ Cervical (140 Isolates)	Zoliflodacin	>=0.5	0.093	0.250	0.008, 0.250	0/140 (0)
	Azithromycin	>=2	0.250	1.000	0.060, 4.000	3/140 (2)
	Cefixime	>=0.25	0.015	0.030	0.002, 0.060	0/140 (0)
	Ceftriaxone	>=0.125	0.008	0.015	0.001, 0.060	0/140 (0)
	Ciprofloxacin	>=1	0.004	2.000	0.001, 16.000	16/140 (11)
	Penicillin	>=2	0.500	2.000	0.030, 64.000	24/140 (17)
	Spectinomycin	>=128	128.000	128.000	128.000, 128.000	0/140 (0)
Rectal (14 Isolates)	Zoliflodacin	>=0.5	0.060	0.250	0.008, 0.250	0/14 (0)
	Azithromycin	>=2	0.250	1.000	0.125, 1.000	0/14 (0)
	Cefixime	>=0.25	0.015	0.030	0.004, 0.060	0/14 (0)
	Ceftriaxone	>=0.125	0.006	0.008	0.001, 0.015	0/14 (0)
	Ciprofloxacin	>=1	0.004	0.008	0.001, 0.008	0/14 (0)
	Penicillin	>=2	0.375	2.000	0.060, 8.000	2/14 (14)
	Spectinomycin	>=128	128.000	128.000	128.000, 128.000	0/14 (0)
Pharyngeal (23 Isolates)	Zoliflodacin	>=0.5	0.125	0.250	0.008, 0.250	0/23 (0)
	Azithromycin	>=2	0.500	1.000	0.060, 2.000	1/23 (4)
	Cefixime	>=0.25	0.015	0.060	0.004, 0.060	0/23 (0)
	Ceftriaxone	>=0.125	0.008	0.030	0.001, 0.060	0/23 (0)
	Ciprofloxacin	>=1	0.004	4.000	0.002, 8.000	5/23 (22)
	Penicillin	>=2	1.000	8.000	0.250, 64.000	9/23 (39)
	Spectinomycin	>=128	128.000	128.000	128.000, 128.000	0/23 (0)

Notes: n=number of subjects at or above MIC breakpoint. N=number of subjects with antimicrobial results for the anatomical site and population being summarized. *MIC breakpoints were defined according to Clinical Laboratory Standards Institute (CLSI) criteria except for azithromycin, zoliflodacin, and ceftriaxone.

Table S4. *N. gonorrhoeae* Antimicrobial Susceptibility of Test of Cure Isolates (Microbiologic Failure Isolates) – (Micro-ITT Population)

Specimen	Antimicrobial	MIC Breakpoint	MIC50 (µg/mL)	MIC90 (µg/mL)	Range (µg/mL)	Proportion at or above MIC Breakpoint n/N (%)
Urethral/ Cervical (3 Isolates)	Zoliflodacin	>=0.5	0.125	0.250	0.060, 0.250	0/3 (0)
	Azithromycin	>=2	0.500	0.500	0.250, 0.500	0/3 (0)
	Cefixime	>=0.25	0.015	0.030	0.004, 0.030	0/3 (0)
	Ceftriaxone	>=0.125	0.008	0.015	0.001, 0.015	0/3 (0)
	Ciprofloxacin	>=1	0.000	2.000	0.004, 2.000	1/3 (33)
	Penicillin	>=2	2.000	64.000	0.250, 64.00	2/3 (67)
	Spectinomycin	>=128	128.000	128.000	128.000, 128.000	0/3 (0)
Rectal (0 Isolates)	Zoliflodacin	>=0.5	-	-	-	-
	Azithromycin	>=2	-	-	-	-
	Cefixime	>=0.25	-	-	-	-
	Ceftriaxone	>=0.125	-	-	-	-
	Ciprofloxacin	>=1	-	-	-	-
	Penicillin	>=2	-	-	-	-
	Spectinomycin	>=128	-	-	-	-
Pharyngeal (6 Isolates)	Zoliflodacin	>=0.5	0.125	0.250	0.060, 0.250	0/6 (0)
	Azithromycin	>=2	0.500	1.000	0.125, 1.000	0/6 (0)
	Cefixime	>=0.25	0.023	0.060	0.008, 0.060	0/6 (0)
	Ceftriaxone	>=0.125	0.012	0.030	0.004, 0.030	0/6 (0)
	Ciprofloxacin	>=1	1.004	16.000	0.002, 16.000	3/6 5(0)
	Penicillin	>=2	1.500	64.000	0.125, 64.000	3/6 (50)
	Spectinomycin	>=128	128.000	128.000	128.000, 128.000	0/6 (0)

Notes: n=number of subjects at or above MIC breakpoint. N=number of subjects with antimicrobial results for the anatomical site and population being summarized. *MIC breakpoints were defined according to Clinical Laboratory Standards Institute (CLSI) criteria except for azithromycin, zoliflodacin, and ceftriaxone.

Figure S1. *N. gonorrhoeae* Antimicrobial Susceptibility of Baseline Isolates - All Sites (Micro-ITT Population) – Heterosexual vs. MSM

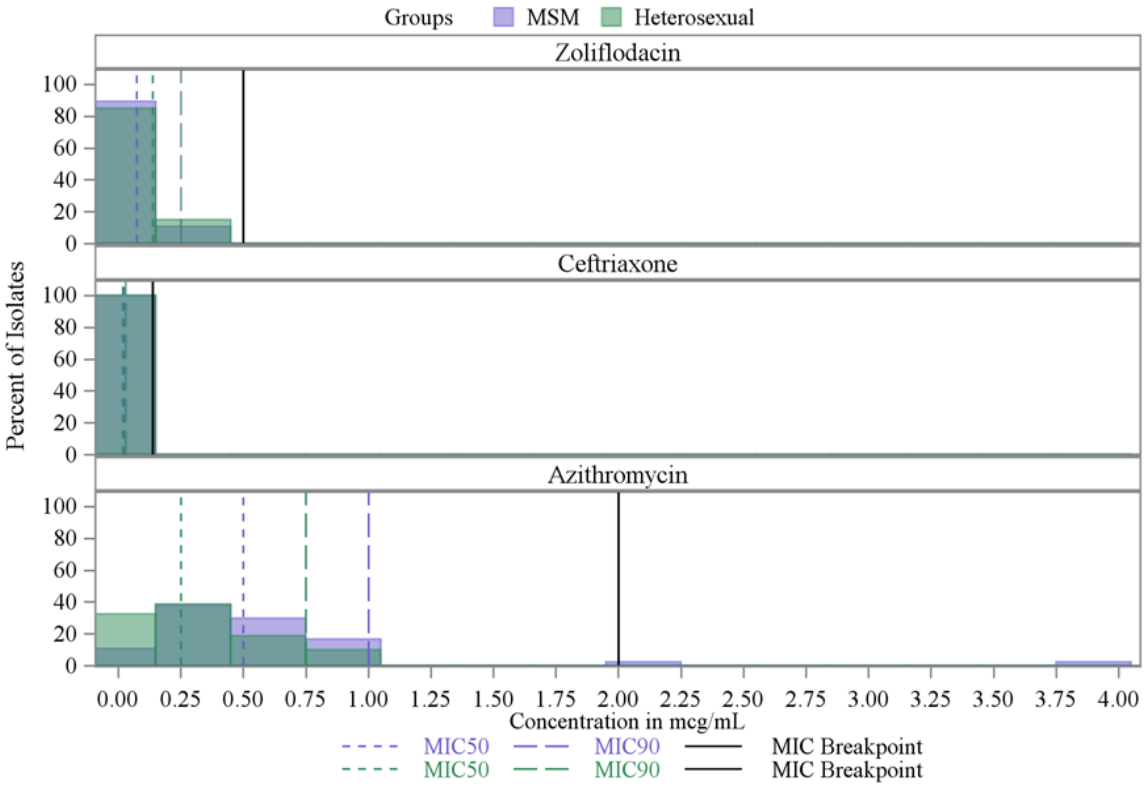

Figure S2. *N.gonorrhoeae* Antimicrobial Susceptibility of Baseline Pharyngeal Isolates (Micro-ITT Population) – Heterosexual vs. MSM

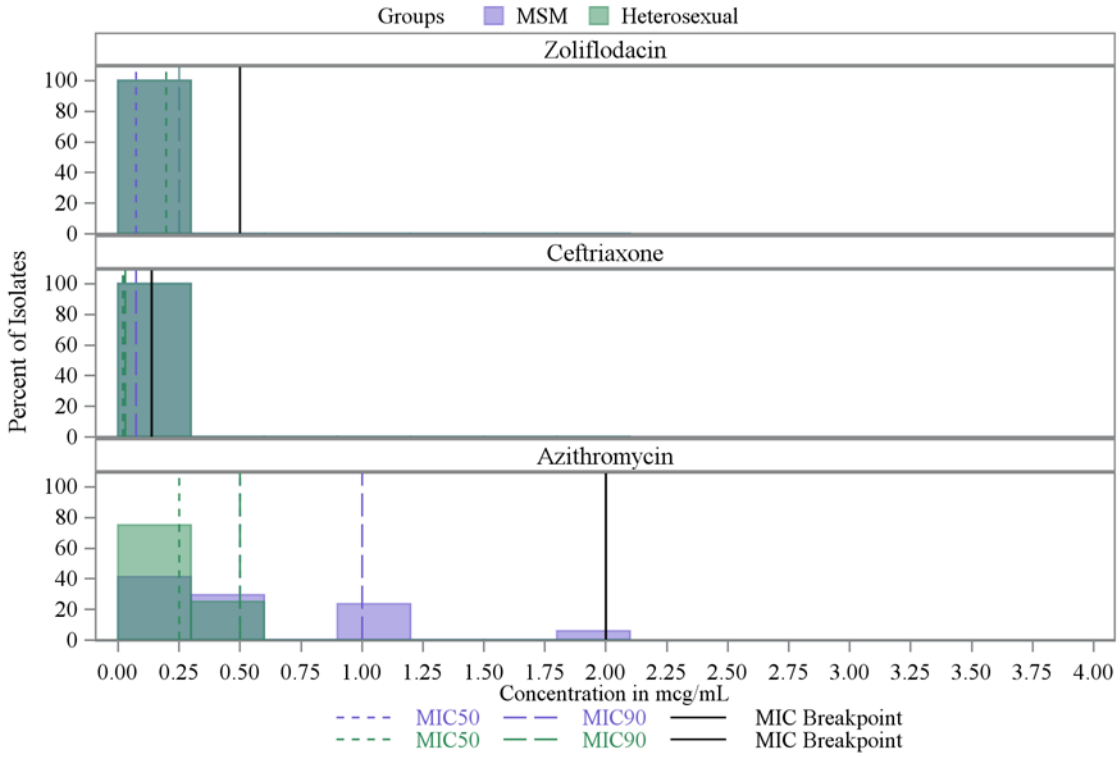

Figure S3. *N. gonorrhoeae* Antimicrobial Susceptibility of Baseline Urogenital Isolates (Micro-ITT Population) – Heterosexual vs. MSM