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

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ABSTRACT

BACKGROUND

Antibiotic-resistant *Neisseria gonorrhoeae* has prompted the development of new therapies. Zoliflodacin is a new antibiotic that inhibits DNA biosynthesis. In this multicenter, phase 2 trial, zoliflodacin was evaluated for the treatment of uncomplicated gonorrhea.

METHODS

We randomly assigned eligible men and women who had signs or symptoms of uncomplicated urogenital gonorrhea or untreated urogenital gonorrhea or who had had sexual contact in the preceding 14 days with a person who had gonorrhea to receive a single oral dose of zoliflodacin (2 g or 3 g) or a single 500-mg intramuscular dose of ceftriaxone in a ratio of approximately 70:70:40. A test of cure occurred within 6±2 days after treatment, followed by a safety visit 31±2 days after treatment. The primary efficacy outcome measure was the proportion of urogenital microbiologic cure in the microbiologic intention-to-treat (micro-ITT) population.

RESULTS

From November 2014 through December 2015, a total of 179 participants (167 men and 12 women) were enrolled. Among the 141 participants in the micro-ITT population who could be evaluated, microbiologic cure at urogenital sites was documented in 55 of 57 (96%) who received 2 g of zoliflodacin, 54 of 56 (96%) who received 3 g of zoliflodacin, and 28 of 28 (100%) who received ceftriaxone. All rectal infections were cured in all 5 participants who received 2 g of zoliflodacin and all 7 who received 3 g, and in all 3 participants in the group that received ceftriaxone. Pharyngeal infections were cured in 4 of 8 participants (50%), 9 of 11 participants (82%), and 4 of 4 participants (100%) in the groups that received 2 g of zoliflodacin, 3 g of zoliflodacin, and ceftriaxone, respectively. A total of 84 adverse events were reported: 24 in the group that received 2 g of zoliflodacin, 37 in the group that received 3 g of zoliflodacin, and 23 in the group that received ceftriaxone. According to investigators, a total of 21 adverse events were thought to be related to zoliflodacin, and most such events were gastrointestinal.

CONCLUSIONS

The majority of uncomplicated urogenital and rectal gonococcal infections were successfully treated with oral zoliflodacin, but this agent was less efficacious in the treatment of pharyngeal infections. (Funded by the National Institutes of Health and Entasis Therapeutics; ClinicalTrials.gov number, NCT02257918.)

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The incidence of gonorrhea in the United States increased by 67% from 2013 through 2017.[1] Concomitantly, the antimicrobial susceptibility of *Neisseria gonorrhoeae* has diminished.[2,3] Decreased susceptibility and increased resistance to macrolides and cephalosporins have been reported in the United States and around the world, and treatment failures have been noted.[4-13] *N. gonorrhoeae* isolates that are resistant to the currently recommended regimen of ceftriaxone and azithromycin have also been reported.[14-16]

The Centers for Disease Control and Prevention (CDC) revised treatment guidelines for gonorrhea three times between 2006 and 2012 in response to both treatment failures and increases in minimum inhibitory concentrations (MICs).[17-21] Unfortunately, no highly reliable, orally administered, and affordable alternative antimicrobial agents with minimal side effects are currently available.

Zoliflodacin (also known as AZD0914 or ETX0914) is an investigational spiropyrimidinetrione antimicrobial agent that has received "qualified infectious disease product" and subsequent "fast track" designations from the Food and Drug Administration (FDA) for development solely as an oral treatment for gonococcal infections. The mechanism of action of zoliflodacin differs from currently available therapies in that it inhibits microbial biosynthesis by arresting the cleaved covalent gyrase complex and the formation of fused circular DNA required for biosynthesis.[22] The effectiveness of this mechanism has been illustrated by the sensitivity of ciprofloxacin-resistant and ceftriaxone-resistant *N. gonorrhoeae* and fluoroquinolone-resistant and vancomycin-resistant *Staphylococcus aureus* isolates to zoliflodacin.[23] Zoliflodacin is also active against *Chlamydia trachomatis*, *Chlamydophila pneumonia*, *Mycoplasma genitalium*, and ureaplasma species.[23] In this multicenter, randomized, open-label, phase 2 trial, we compared the efficacy and safety of a single dose of 2 g or 3 g of oral zoliflodacin with 500 mg of intramuscular ceftriaxone for the treatment of uncomplicated urogenital gonorrhea.

Materials and Methods

Oversight

This trial was conducted with approvals from the FDA, the European Medicines Agency, and the institutional review boards at each site. An independent data and safety monitoring board reviewed the safety data. Entasis Therapeutics provided the zoliflodacin, and the Division of Microbiology and Infectious Diseases (DMID) at the National Institutes of Health provided the trial design. The initial draft of the manuscript was written by the first author. No paid medical writers participated in manuscript preparation. All authors had access to the data and vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org.

Participating Sites and Eligibility

Eligible persons were enrolled at sexual health clinics in New Orleans, Seattle, and Indianapolis and in Birmingham, Alabama, and Durham, North Carolina. Men and nonpregnant women 18 to 55 years of age were eligible to participate if they had signs and symptoms of urogenital gonorrhea, untreated urogenital gonorrhea, or sexual contact in the preceding 14 days with a person who had gonorrhea. Other inclusion criteria were the ability to provide written informed consent, negative results on a urine pregnancy test, abstinence from sexual intercourse with or without condom use for 7 days after treatment, use of a contraceptive (if of child-bearing potential) for 30 days before and after treatment, and condom use with another contraceptive for 30 days after treatment.

Exclusion criteria were complicated gonorrhea (as indicated by pelvic inflammatory disease, epididymitis, or other conditions), use of systemic or intravaginal antibiotics or antiviral agents within 30 days before enrollment, known allergy to cephalosporin or penicillin, or known coinfection with chlamydia at the time of enrollment. Initially, known infection with the human immunodeficiency virus (HIV) was a criterion for exclusion, but this criterion was later modified to apply only to HIV-infected persons who were receiving antiretroviral therapy to avoid potential drug interactions with zoliflodacin. Other criteria for exclusion from the trial are available in Table S1 in the Supplementary Appendix, available at NEJM.org.

Trial Design

Zoliflodacin is a powder formulated for oral suspension. Suspensions were prepared by a central

pharmacy in doses of 2 g and 3 g and then shipped and stored frozen. After thawing, the suspension was administered under direct observation by trial investigators.

Participants were randomly assigned to receive single, oral doses of 2 g or 3 g of zoliflodacin or a single intramuscular dose of 500 mg of ceftriaxone. This ceftriaxone dose (twice the dose recommended by the CDC) was used to meet the regulatory requirements of both the FDA and the European Medicines Agency and to correspond with the recommended European dose.[24-26]

At enrollment, specimens were obtained from urethral, cervical, pharyngeal, and rectal sites for *N. gonorrhoeae* culture and nucleic acid amplification testing (NAAT). Adverse events were graded with the use of toxicity tables that were based on the DMID comprehensive toxicity tables (20NOV2013) and modified for this trial. Adverse events were followed through the final safety visit at 31±2 days.

Participants with negative gonococcal cultures could not be evaluated for the efficacy of zoliflodacin but were followed for safety. Participants who had persistent genital symptoms (clinical failure) or positive results from gonococcal cultures of samples obtained at any anatomical site (microbiologic failure) at test-of-cure visits received further treatment in accordance with the local standard of care. Participants who had positive test results for *C. trachomatis* on samples obtained at enrollment were also treated at the test-of-cure visit.

RANDOMIZATION

After written informed consent was obtained and eligibility for participation was assessed, participants were randomly assigned in a 70:70:40 ratio to receive either 2 g or 3 g of zoliflodacin or 500 mg of ceftriaxone. We used a permuted-block randomization scheme stratified according to trial site and prepared at the Statistical and Data Coordinating Center at Emmes.

ESTIMATION OF SAMPLE SIZE

The trial was designed to evaluate the safety of zoliflodacin and to inform the decision to proceed to a phase 3 trial. The enrollment goal was 144 participants with positive baseline urethral or cervical cultures for *N. gonorrhoeae*. Assuming that 20% of potential participants would not be eligible, the target enrollment was 180 participants. An allocation ratio for the two zoliflodacin groups and the ceftriaxone group of 70:70:40 was anticipated to result in at least 30 participants in the ceftriaxone group while maximizing the size of zoliflodacin groups for evaluation of safety.

CLINICAL AND MICROBIOLOGIC PROCEDURES

Urethral, cervical, pharyngeal, and rectal swabs were collected for gonococcal culture and NAAT at enrollment, before administration of the trial drug. At the test-of-cure (day 6±2) and safety visits (day 31±2), repeat cultures and swabs for NAAT were obtained from all anatomical sites regardless of the participant's history of sexual contact or baseline culture results at enrollment. NAAT was performed at local laboratories or at the Infectious Diseases Laboratory at the University of Alabama at Birmingham (UAB) with the use of Aptima Combo 2 (Hologic).

For culture, modified Thayer–Martin agar plates were inoculated and immediately placed in a carbon-dioxide–enriched environment before transport to local laboratories. Plates were read at 24, 48, and 72 hours after inoculation. Colonies containing oxidase-positive, gram-negative diplococci were presumed to be *N. gonorrhoeae.* Isolates were frozen and shipped to the UAB laboratory, where the identification of neisseria, hemophilus, moraxella, and related bacteria was confirmed with the use of the Remel RapID NH System.

Agar dilution was used to determine bacterial susceptibilities to zoliflodacin, azithromycin, cefixime, ceftriaxone, ciprofloxacin, penicillin, and spectinomycin. MIC breakpoints were defined in accordance with the criteria of the Clinical and Laboratory Standards Institute for all drugs with the exception of azithromycin, zoliflodacin, and ceftriaxone.[27] Lower MIC breakpoints of 2.0 μg per milliliter and 0.5 μg per milliliter were used for azithromycin and zoliflodacin, respectively. For ceftriaxone, the lower breakpoint of 0.125 μg per milliliter was used, as defined by the Gonococcal Isolate Surveillance Project.

OUTCOME AND EFFICACY MEASURES

The primary efficacy measure (microbiologic cure) was the proportion of participants with urogenital infection who had conversion from a positive baseline *N. gonorrhoeae* culture to a nega-

tive culture at the test-of-cure visit. The primary outcome measure of safety was the proportion of participants reporting adverse events and serious adverse events related to the trial drug through the third visit.

Secondary efficacy outcome measures included the proportion of participants with pharyngeal or rectal microbiologic cure; the proportion with negative results for *N. gonorrhoeae* on NAAT from swabs obtained from urethral, cervical, rectal, or pharyngeal sites; the proportion of participants with clinical cure (resolution of signs and symptoms of gonococcal infection); and MICs of *N. gonorrhoeae* against zoliflodacin and ceftriaxone at baseline and test of cure.

ANALYSIS POPULATIONS

The microbiologic intention-to-treat (micro-ITT) population included all participants with gonorrhea at urethral or cervical sites who underwent randomization at enrollment. The outcome for participants who did not return for test-of-cure visits was classified as treatment failure. Participants with negative cultures for *N. gonorrhoeae* from urethral or cervical sites at enrollment were excluded from the micro-ITT analysis. Participants with negative cultures for *N. gonorrhoeae* at rectal or pharyngeal sites at enrollment were excluded from the micro-ITT population for corresponding analyses for secondary efficacy end points.

The per-protocol efficacy population included participants in the micro-ITT population who met all criteria for inclusion, did not have concomitant infection other than chlamydia or bacterial vaginosis, did not receive any other systemic antibiotic before test of cure, and returned for a test-of-cure visit within the window of 6±2 days.

STATISTICAL ANALYSIS

Primary and secondary efficacy end points were assessed in the micro-ITT populations and were repeated as secondary analyses in the per-protocol population. Point estimates for treatment-group-specific proportions and difference in proportions between the zoliflodacin and ceftriaxone groups with corresponding 95% confidence intervals were calculated. All P values and confidence intervals are two-sided. Additional descriptive analyses for primary and secondary efficacy outcomes were performed according to treatment group. MIC distributions were summarized for each treatment group and anatomical site at baseline and test-of-cure visits. Median, 90th percentile, and range of MICs are reported. Adverse events were summarized in accordance with the *Medical Dictionary for Regulatory Activities* (MedDRA) version 18, preferred term and system organ class. The proportion of participants with and the exact 95% confidence interval for adverse events were computed in aggregate and in accordance with MedDRA categories. Serious adverse events were reported in accordance with MedDRA coding; the dates of treatment, onset, and resolution; severity; relatedness; and outcomes. Hematologic, hepatic, and renal laboratory results related to safety were assessed at enrollment and at test-of-cure and safety visits and were then summarized according to grade and treatment group. Standard summary statistics, including means and 95% confidence intervals, were computed. All statistical tests used 95% confidence intervals for binomial proportions, and differences in binomial proportions were computed with the use of Clopper–Pearson confidence limits.[28] Analyses were conducted with SAS software, version 9.3 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

Between November 2014 and December 2015, we screened 181 persons; 179 persons (167 men and 12 women) underwent randomization and were treated (Fig. 1 and Table 1). Four HIV-infected participants were enrolled. Thirty-eight participants were excluded from the efficacy analysis owing to negative urethral or cervical gonococcal cultures. Among the remaining 141 participants, 28 received 500 mg of ceftriaxone, 57 received 2 g of zoliflodacin, and 56 received 3 g of zoliflodacin. Participants in the micro-ITT populations who could be evaluated included 141 with positive urethral or cervical cultures, 23 with positive pharyngeal cultures, and 15 with positive rectal cultures. Participants in the per-protocol population who could be evaluated included 117 with positive urethral cultures, 19 with positive pharyngeal cultures, and 13 with positive rectal cultures. All 179 participants completed the test-of-cure visit.

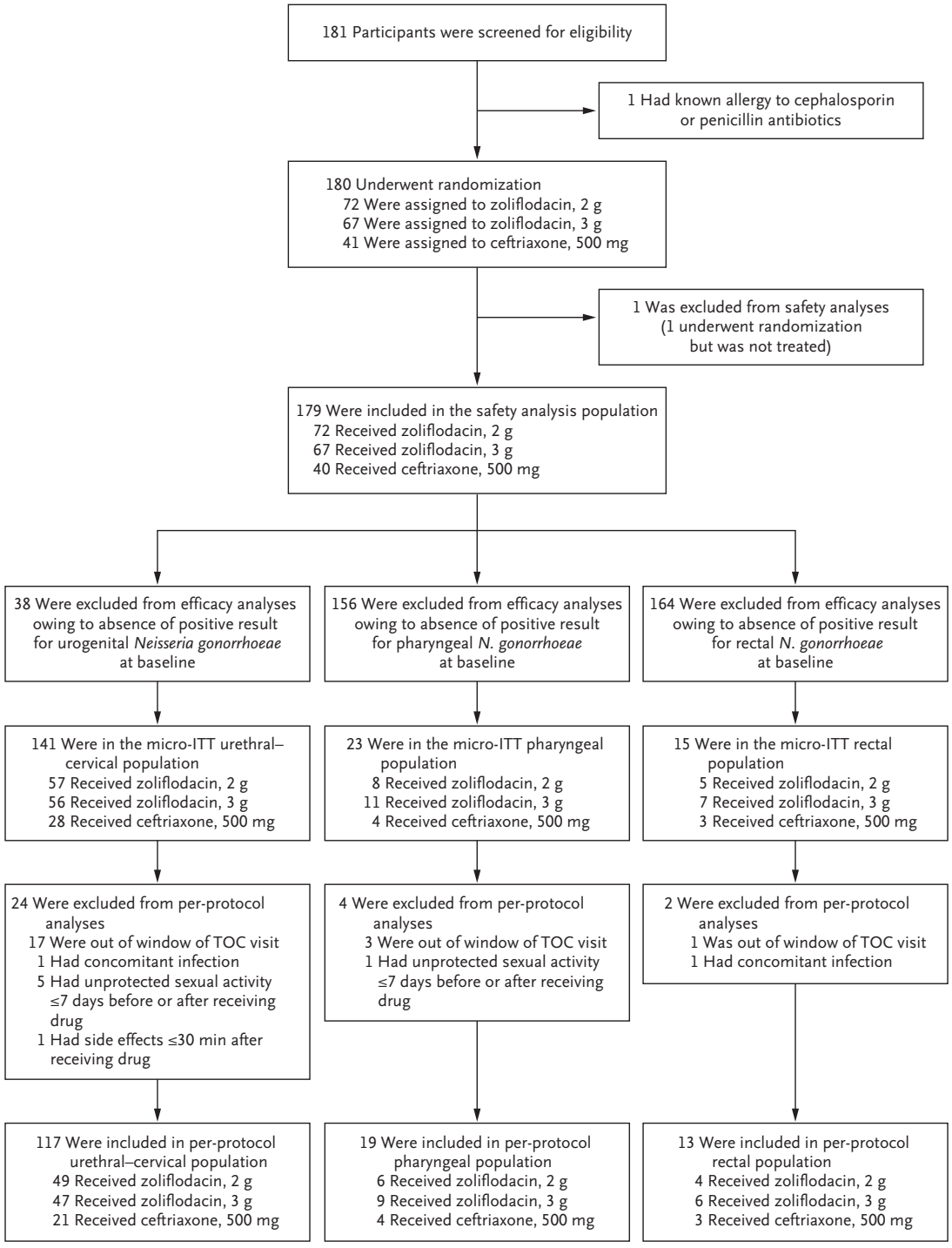

Figure 1. Screening, Randomization, and Treatment.

The phrase "out of window of TOC [test of cure]" refers to a participant who returned outside the time frame of 6±2 days specified in the protocol. Micro-ITT denotes microbiologic intention to treat.

Table 1. Selected Baseline Characteristics of Participants According to Trial Site.*

Characteristic	University of Washington (N=66)	Louisiana State University (N=46)	Indiana University (N=34)	University of Alabama (N=22)	University of North Carolina (N=12)	All Sites (N=180)
Age						
Mean	29.7±8.3	28.4±8.1	30.2±10.1	25.8±5.1	27.5±6.3	28.8±8.2
Median (IQR)	27 (19–53)	27 (18–53)	27 (18–53)	26 (19–40)	27 (18–42)	27 (18–53)
Sex — no. (%)						
Male	64 (97)	46 (100)	34 (100)	13 (59)	10 (83)	167 (93)
Female†	2 (3)	0	0	9 (41)	2 (17)	13 (7)
Race — no. (%)						
Black	15 (23)	34 (74)	26 (76)	22 (100)	10 (83)	107 (59)
White	42 (64)	10 (22)	5 (15)	0	1 (8)	58 (32)
Other, multiracial, or unknown‡	9 (14)	2 (4)	3 (9)	0	1 (8)	15 (8)
Ethnicity — no. (%)						
Non-Hispanic	59 (89)	44 (96)	33 (97)	22 (100)	9 (75)	167 (93)
Hispanic	7 (11)	2 (4)	1 (3)	0	3 (25)	13 (7)
Sexual partner of male participants — no. (%)						
Women only	13 (20)	30 (65)	26 (76)	13 (100)	8 (80)	90 (54)
Men only	45 (70)	13 (28)	6 (18)	0	2 (20)	66 (40)
Men and women	6 (9)	3 (7)	2 (6)	0	0	11 (7)

* Plus–minus values are means ±SD. The denominators for percentages are based on the number of participants enrolled, with the exception of the sexual partner summaries, and represent the number of men or women enrolled in the trial for each therapy. Percentages may not total 100 because of rounding. IQR denotes interquartile range.

† One woman was randomly assigned to a trial group and was subsequently found to be pregnant and thus was not treated. Among the 12 women in the trial who underwent randomization and received treatment (7% of the total population), all 12 reported having sex with men.

‡ The category of "other, multiracial, or unknown" included 9 participants who were multiracial, 3 who were Asian, 1 who was an American Indian–Alaskan Native, 1 who was a Hawaiian–Pacific Islander, and 1 whose racial identity was unknown. Race and ethnic group were reported by the participants.

EFFICACY

At enrollment, 179 gonococcal infections were detected; these infections occurred in the urethra, cervix, rectum, or pharynx. Microbiologic cure rates are presented according to anatomical site and treatment group in Table 2.

In the micro-ITT population, urogenital infections were cured in 55 of 57 participants (96%) in the group that received 2 g of zoliflodacin, 54 of 56 participants (96%) in the group that received 3 g of zoliflodacin, and 28 of 28 participants (100%) in the group that received 500 mg of ceftriaxone. In the per-protocol analyses, 48 of 49 (98%), 47 of 47 (100%), and 21 of 21 (100%) of the participants in these respective groups had microbiologic cure. All rectal infections in all groups were cured. Pharyngeal gonorrhea was cured in 4 of 8 patients (50%) in the group that received 2 g of zoliflodacin and 9 of 11 patients (82%) in the group that received 3 g of zoliflodacin. All four pharyngeal infections in the ceftriaxone group were cured (Table 2). In 3 HIV-infected participants, *N. gonorrhoeae* was isolated only from urogenital sites, and these infections were cured.

CLINICAL CURE

In the micro-ITT population, among participants with signs and symptoms of *N. gonorrhoeae* infection at baseline, cure occurred in 52 of 57 participants (91%; 95% confidence interval [CI], 80 to 97) in the group that received 2 g of zoliflodacin,

46 of 49 participants (94%; 95% CI, 83 to 99%) in the group that received 3 g of zoliflodacin, and 26 of 27 participants (96%; 95% CI, 81 to 100) in the group that received ceftriaxone. Clinical cure rates were similar in the per-protocol population.

CLEARANCE OF *N. GONORRHOEAE* NUCLEIC ACID AT TEST OF CURE

As assessed on NAAT, nucleic acid clearance occurred in the micro-ITT population in 48 of 57 participants (84%; 95% CI, 72 to 93) in the group that received 2 g of zoliflodacin, 42 of 52 participants (81%; 95% CI, 67 to 90) in the group that received 3 g of zoliflodacin, and 25 of 28 participants (89%; 95% CI, 71 to 98) in the group that received ceftriaxone. All participants with rectal gonorrhea detected on NAAT at enrollment had nucleic acid clearance at the test-of-cure visit. Nucleic acid clearance at test of cure was lowest in the pharynx, in 2 of 8 participants (25%) in the group that received 2 g of zoliflodacin, 6 of 11 (55%) in the group that received 3 g of zoliflodacin, and 2 of 4 (50%) in the group that received ceftriaxone. Findings were similar in the per-protocol population.

SAFETY AND ADVERSE EVENTS

A total of 84 adverse events (24 in the group that received 2 g of zoliflodacin, 37 in the group that received 3 g of zoliflodacin, and 23 in the ceftriaxone group) were reported by 59 participants (33%). The events included 11 moderate and 1 serious adverse event, a nonfatal gunshot wound considered by the investigators to be unrelated to zoliflodacin (Table 3, and Table S2 in the Supplementary Appendix). A total of 21 participants reported adverse events that investigators assessed as being related to zoliflodacin; most such events were gastrointestinal and self-limiting (5 events occurred in the group that received 2 g of zoliflodacin and 8 events occurred in the group that received 3 g of zoliflodacin).

ANTIMICROBIAL SUSCEPTIBILITY TESTING

No isolate at baseline or test of cure had MICs of zoliflodacin that were above the breakpoint (Tables S3 and S4 in the Supplementary Appendix). Baseline isolate MICs at or above breakpoints were noted for azithromycin, penicillin, and ciprofloxacin in the micro-ITT population.

Table 2. Microbiologic Cure Rates at Test-of-Cure Visit — Micro-ITT and Per-Protocol Populations.

Population, Site, and Treatment	Confirmed Infections	Cures	Microbiologic Cure
	number		*% (95% CI)*
Micro-ITT			
Urethra or cervix			
Zoliflodacin, 2 g	57	55	96 (88–100)
Zoliflodacin, 3 g	56	54	96 (88–100)
Ceftriaxone, 500 mg	28	28	100 (88–100)
Rectum			
Zoliflodacin, 2 g	5	5	100 (48–100)
Zoliflodacin, 3 g	7	7	100 (59–100)
Ceftriaxone 500 mg	3	3	100 (29–100)
Pharynx			
Zoliflodacin, 2 g	8	4	50 (16–84)
Zoliflodacin, 3 g	11	9	82 (48–98)
Ceftriaxone, 500 mg	4	4	100 (40–100)
Per protocol			
Urethra or cervix			
Zoliflodacin, 2 g	49	48	98 (89–100)
Zoliflodacin, 3 g	47	47	100 (92–100)
Ceftriaxone, 500 mg	21	21	100 (84–100)
Rectum			
Zoliflodacin, 2 g	4	4	100 (40–100)
Zoliflodacin, 3 g	6	6	100 (54–100)
Ceftriaxone, 500 mg	3	3	100 (29–100)
Pharynx			
Zoliflodacin, 2 g	6	4	67 (22–96)
Zoliflodacin, 3 g	9	7	78 (40–97)
Ceftriaxone, 500 mg	4	4	100 (40–100)

Among a total of 140 baseline urethral or cervical isolates for which there were results for MICs, 24 (17%), 16 (11%), and 3 (2%) had MICs at or above the breakpoint for penicillin, ciprofloxacin, and azithromycin, respectively (Table S3 in the Supplementary Appendix). Among 14 baseline rectal isolates for which there were MIC results, 2 (14%) had MICs at or above the breakpoint for penicillin. Among 23 baseline pharyngeal isolates for which there were MIC results, 9 (39%), 5 (22%), and 1 (4%) isolates had MICs at or above the breakpoint for penicillin, ciprofloxacin, and azithromycin, respectively. (Table 4 summarizes

Table 3. Participants with Adverse Events According to MedDRA System Organ Class, Severity, Relationship to Trial Drug, and Treatment.*

MedDRA System Organ Class	Zoliflodacin, 2 g (N=72)					Zoliflodacin, 3 mg (N=67)					Ceftriaxone, 500 mg (N=40)				
	Severity†			Relationship to Trial Drug†		Severity†			Relationship to Trial Drug†		Severity†			Relationship to Trial Drug†	
	Mild	*Moderate*	*Severe*	*Not Related*	*Related*	*Mild*	*Moderate*	*Severe*	*Not Related*	*Related*	*Mild*	*Moderate*	*Severe*	*Not Related*	*Related*
	number (percent)														
Any system organ class	14 (19)	4 (6)	0	9 (13)	9 (13)	20 (30)	3 (4)	1 (1)	12 (18)	12 (18)	14 (35)	4 (10)	0	12 (30)	6 (15)
Gastrointestinal disorders	5 (7)	0	0	1 (1)	4 (6)	8 (12)	0	0	1 (1)	7 (10)	3 (8)	0	0	1 (3)	2 (5)
General disorders	1 (1)	0	0	0	1 (1)	0	0	0	0	0	2 (5)	0	0	1 (3)	1 (3)
Investigations	1 (1)	3 (4)	0	2 (3)	2 (3)	1 (1)	1 (1)	0	2 (3)	0	0	1 (3)	0	1 (3)	0
Nervous-system disorders	0	0	0	0	0	6 (9)	0	0	1 (1)	5 (7)	2 (5)	0	0	1 (3)	1 (3)

* A complete list of adverse events is available in Table S2 in the Supplementary Appendix. MedDRA denotes *Medical Dictionary for Regulatory Activities*.
† With regard to severity and relationship to trial drug, a participant is counted only once per preferred term.

the antimicrobial susceptibility of isolates according to anatomical site.)

Among participants in whom there was microbiologic treatment failure, test-of-cure MICs were at or above the breakpoints for penicillin and ciprofloxacin (Table S4 in the Supplementary Appendix). Among the four cases of urethral or cervical infection for which there were MIC results, two isolates had MICs at or above the breakpoint for penicillin and one isolate had an MIC that was at or above the breakpoint for ciprofloxacin. Among participants in whom therapy failed, there were no statistically significant changes in gonococcal pretreatment or posttreatment MICs. The MIC for one pharyngeal isolate in a participant treated with ceftriaxone increased from 0.001 μg per milliliter at baseline to 0.004 μg per milliliter at the test-of-cure visit, but the MIC did not reach the breakpoint.

There was no statistically significant difference between heterosexual participants and men who had sex with men with respect to the susceptibility of *N. gonorrhoeae* isolates to zoliflodacin at baseline or test of cure. A difference in susceptibility to azithromycin between these groups was noted (Figs. S1, S2, and S3 in the Supplementary Appendix).

DISCUSSION

Zoliflodacin was effective in treating gonococcal urogenital and rectal infections. In the micro-ITT population, 96% of infected participants in the group that received a single oral dose of 2 g of zoliflodacin and in the group that received 3 g of zoliflodacin had microbiologic cure at urogenital sites. Although there were few participants with rectal infections, all had microbiologic cure. The efficacy of zoliflodacin was lower among participants with pharyngeal infections than among those with urogenital and rectal infections.

Zoliflodacin was not as effective as ceftriaxone in treating pharyngeal gonorrhea, which is generally more difficult to treat than urethral, cervical, or rectal gonorrhea. Currently, this limitation has not curtailed recommendations for the use of drugs such as spectinomycin or fluoroquinolones for the treatment of gonorrhea.[29-31] In previous studies, pharyngeal isolates obtained from participants in whom treatment was not successful did not show antibiotic resistance or

Table 4. Comparison of Zoliflodacin with Currently Recommended Antimicrobials for the Treatment of Gonorrhea According to Site of Infection (Micro-ITT Population).*

Specimen and Antimicrobial Drug	MIC Breakpoint	MIC50 (μg/ml)	MIC90 (μg/ml)	Range (μg/ml)	Proportion at or above MIC Breakpoint
					no./total no. (%)
Urethra or cervix — 140 isolates					
Zoliflodacin	≥0.5	0.093	0.250	0.008–0.250	0/140
Azithromycin	≥2	0.250	1.000	0.060–4.000	3/140 (2)
Ceftriaxone	≥0.125	0.008	0.015	0.001–0.060	0/140
Rectum — 14 isolates					
Zoliflodacin	≥0.5	0.060	0.250	0.008–0.250	0/14
Azithromycin	≥2	0.250	1.000	0.125–1.000	0/14
Ceftriaxone	≥0.125	0.006	0.008	0.001–0.015	0/14
Pharynx — 23 isolates					
Zoliflodacin	≥0.5	0.125	0.250	0.008–0.250	0/23
Azithromycin	≥2	0.500	1.000	0.060–2.000	1/23
Ceftriaxone	≥0.125	0.008	0.030	0.001–0.060	0/23

* Values for minimum inhibitory concentration (MIC) were defined as the lowest concentration of the antibiotic at which 90% (MIC90) and 50% (MIC50) of the isolates were inhibited.

meaningful change in antimicrobial susceptibility after treatment,[29,31] as we observed in this trial. Thus, it has been speculated that poor drug penetration into pharyngeal tissue may be responsible for most pharyngeal treatment failures rather than reinfection or resistant organisms.[29]

The traditional criterion for a recommendation of antibiotics for uncomplicated urogenital gonorrhea is a cure rate of more than 95%, with the lower boundary of the confidence interval greater than 95%.[32] To be recommended as an alternative, the cure rate must be higher than 95%, with the lower boundary of the confidence interval higher than 90%.[32] Although the cure rates for 2 g of zoliflodacin, 3 g of zoliflodacin, and 500 mg of ceftriaxone met the point-estimate criteria for efficacy at the urogenital and rectal sites, only ceftriaxone met that criterion for the pharyngeal site. In our trial, the criteria for the lower boundaries of the confidence intervals were not met by either zoliflodacin or ceftriaxone for any anatomical site.

Microbiologic cure was defined on the basis of negative gonococcal cultures instead of NAATs. Regulatory agencies have preferred culture over NAAT for the assessment of cure because of the concern that residual nucleic acids from dead organisms may remain after successful therapy. Therefore, an NAAT obtained at a test-of-cure visit may result in false positive results and an inability to determine microbiologic cure.

The most common adverse events associated with zoliflodacin were gastrointestinal in nature. Although this trial did not involve a head-to-head comparison, there appear to be fewer gastrointestinal effects with zoliflodacin than with other antibiotics currently recommended for uncomplicated gonorrhea.[33-35] Larger, more detailed studies are needed to define this aspect of the side-effect profile of zoliflodacin.

The limitations of our trial include low enrollment of women and participants with rectal infections, as noted in other trials of drugs for the treatment of gonorrhea conducted within the past few years.[34,35] The enrollment of women in trials of new drugs for the treatment of gonorrhea is challenging because of exclusions related to the use of contraceptives. Although there were few cases of rectal gonorrhea in our trial, all were successfully treated. This trial evaluated a single drug to allow the necessary comparative evaluation of efficacy, side-effect profile, and

safety. However, current U.S. and European guidelines recommend dual therapy for gonorrhea — theoretically, to slow the development of antimicrobial resistance and to treat concomitant chlamydial infection. Should the development of zoliflodacin for gonorrhea therapy be pursued, its use in combination with another active agent would probably be the goal.

N. gonorrhoeae has developed resistance to every class of antibiotic recommended for treatment, which now includes cephalosporins and macrolides. Reports of multidrug-resistant *N. gonorrhoeae* and the possibility of untreatable gonorrhea underscore the need for the development of new antimicrobial agents. This phase 2 trial creates equipoise for larger, more definitive studies of zoliflodacin.

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