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Randomized, Double-Blind, Multicenter Safety and Efficacy Study of Rifalazil Compared with Azithromycin for Treatment of Uncomplicated Genital *Chlamydia trachomatis* Infection in Women

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A randomized, double-blind study comparing single-dose chlamydia therapies of oral rifalazil (25 mg) and azithromycin (1 g) was conducted in 82 women with uncomplicated genital *Chlamydia trachomatis* infection. The microbiologic cure rate of *C. trachomatis* with rifalazil ($n = 33$) was 84.8% at the visit on day 22 to 26 (test-of-cure visit), versus 92.1% with azithromycin ($n = 38$), and the number of treatment failures in each group was 5 and 3, respectively. The difference in cure rate was -7.3% , with a lower limit of the 95% confidence interval (95% CI) of -22.5 , and thus, noninferiority was not established at the prespecified margin (lower limit of CI of -15%). The overall treatment-emergent adverse event (TEAE) and treatment-related TEAE rates were lower in the rifalazil group (68% and 55%) than in the azithromycin group (71% and 62%), respectively. Subjects classified as treatment failures at day 22 to 26 had a lower mean plasma concentration of rifalazil at the visit on day 8 to 12 than those classified as treatment cures, but this difference was not significant; however, the levels were similar for both groups at the visit on day 22 to 26. A single 25-mg dose of rifalazil was well tolerated and eradicated *C. trachomatis* in most of these women with uncomplicated genital *C. trachomatis* infection. (The study was registered at clinicaltrials.gov under registration no. NCT01631201).

Chlamydia trachomatis infection is the most frequently reported bacterial sexually transmitted infection (STI) in the United States, with almost 1.5 million cases reported to the Centers for Disease Control and Prevention (CDC) in 2011, which represents the largest number of cases ever reported to the CDC for any condition (1). In women, untreated chlamydia can cause serious sequelae, such as pelvic inflammatory disease, infertility, and ectopic pregnancy (2). The CDC's recommended treatment for uncomplicated *C. trachomatis* infection is either a 1-g single dose of azithromycin or 100 mg of doxycycline twice daily for 7 days (3). A meta-analysis of chlamydia treatment trials showed that the recommended azithromycin and doxycycline regimens had comparable microbiological efficacies (97% versus 98%, respectively) (4). However, most trials used chlamydia culture for test of cure, rather than the more sensitive nucleic acid amplification tests (NAATs) recommended by the CDC (3). Two recent observational studies in women and a nongonococcal urethritis treatment study in symptomatic men, which used NAAT, showed lower cure rates with azithromycin than were previously observed (5–7). Additionally, despite the availability of effective treatment for the management of uncomplicated chlamydial genital infection, repeat infection commonly occurs (7–9). Therefore, more effective chlamydia treatments are needed, ideally administered as a single dose to ensure treatment adherence. Since the approval of azithromycin for the treatment of chlamydia, no new drugs have been approved for *C. trachomatis* infection except for the new once-a-day formulation of doxycycline hyclate (10).

Rifalazil is a rifamycin with potent *in vitro* bactericidal activity against *C. trachomatis*, including persistent forms. *In vitro* studies have shown that rifalazil has a significantly greater antimicrobial

potency against *C. trachomatis* than azithromycin, with their MIC₉₀s being 0.00025 and 0.125 $\mu\text{g/ml}$, respectively (11–13). Rifalazil has a long elimination half-life of approximately 100 h and achieves high intracellular concentrations (11), which could reduce the likelihood of treatment failure and lessen the incidence of repeat infections. The clinical benefit of a single oral dose of 25 mg of rifalazil in treating *C. trachomatis* was demonstrated in a phase II clinical study which enrolled men with nongonococcal urethritis (NGU) (14). Based on data on file with the sponsor, the drug showed an acceptable tolerability profile in 486 individuals who had previously received single or multiple oral doses of rifalazil ranging from 2.5 mg to 275 mg.

We hypothesized that a single oral 25-mg dose of rifalazil would be as effective as a single 1-g dose of azithromycin in the treatment of uncomplicated genital chlamydial infection in women and evaluated this in a randomized, double-blind, multicenter study.

MATERIALS AND METHODS

This was a randomized, double-blind study (clinicaltrials.gov registration no. NCT01631201) designed to evaluate the safety and efficacy of a single

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oral administration of 25 mg of rifalazil compared with a single oral administration of 1 g of azithromycin. The study was conducted at five U.S. study sites and approved by a central IRB, the Western Institutional Review Board (WIRB). It was performed in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. Written informed consent was received from all subjects before study initiation.

Genital chlamydial infection in subjects was defined as having a vaginal swab test positive for *C. trachomatis* based on the Gen-Probe Aptima combo 2 nucleic acid amplification test (NAAT), which was performed by ACM Global at Rochester, NY according to the manufacturer's (Gen-Probe, San Diego, CA) instructions; *Neisseria gonorrhoeae* testing was also performed on the same vaginal swab with the same NAAT. The main inclusion criteria were as follows: women aged ≥ 19 years who were not pregnant or lactating and who were diagnosed with uncomplicated genital *C. trachomatis* infection in the 21 days before randomization based on a positive NAAT. The main exclusion criteria were ≥ 3 episodes of *C. trachomatis* infection within 6 months prior to enrollment or known to have gonorrhea, HIV, syphilis, or active hepatitis B or C virus infection at the time of enrollment. Additionally, women who had taken antimicrobial therapy with activity against *C. trachomatis*, herbal supplements such as St. John's wort and black cohosh, another investigational drug, or antacids (if the medication was used on a daily basis or occasionally but the last dose was on the day of enrollment) within 4 weeks of study enrollment were also excluded.

The study was unpowered and had a planned sample size of 80 subjects, which was considered adequate to characterize the efficacy and safety profiles of rifalazil in a phase 2b study. Subjects were randomized on a 1:1 basis to one of the two treatment groups. There were four scheduled clinic visits, as follows: baseline visit (day 1); visit 2 (on day 8 to 12); visit 3, or test-of-cure (TOC) visit (on day 22 to 26); and visit 4, or end-of-study visit (on day 36 to 40). There was one scheduled telephone contact on day 2 or 3 for all subjects for safety evaluations.

To maintain the blind, all study medications were overencapsulated. Each subject received two capsules of study medication administered as a single oral dose. Study medications were administered at the clinic 15 to 30 min after the consumption of a snack containing $\approx 30\%$ fat (a Zone-Perfect bar) and an 8-ounce glass of water.

The primary efficacy analysis was based on the microbiological intent-to-treat (mITT) population, defined as all randomized subjects who had received the study medication and had a positive *C. trachomatis* NAAT at baseline; subjects also testing positive for *N. gonorrhoeae* at baseline were not excluded from analysis. Subjects who tested positive for *N. gonorrhoeae* at baseline were to be treated with a single intramuscular dose of 250 mg of ceftriaxone. Safety analysis was performed on all subjects who received study medication; the safety population was the same as the intent-to-treat (ITT) population.

The primary efficacy endpoint was the rate of microbiologic cure of *C. trachomatis* at the TOC visit (visit 3, day 22 to 26). The following definitions were used to assess the vaginal swab results: microbiologic cure if *C. trachomatis* was not detected at visit 3, persistence if *C. trachomatis* was detected at visit 3, and unevaluable if subject did not return for the visit, refused further testing, or could not be evaluated for any other reason. Persistence and unevaluable categories were considered microbiologic failure for the primary efficacy analysis. Secondary efficacy analysis to compare the cure rate at visit 4 (on day 36 to 40) was performed similarly to the primary analysis. Treatment failure at visit 3 was carried over as treatment failure for visit 4, even if the *C. trachomatis* test result was negative at visit 4.

The primary and secondary efficacy analyses were a noninferiority comparison between the cure rates of rifalazil and azithromycin. A two-sided 95% confidence interval (95% CI) of the difference in the cure rates (rifalazil-azithromycin) with a 0.05 significance level was computed, and noninferiority was established when the lower limit of the CI was above -15% of the prespecified noninferiority margin. Safety evaluations were

performed on all treated subjects and included examination of adverse event (AE) rates and frequency of laboratory abnormalities. "Treatment-emergent adverse event" (TEAE) denotes an adverse event that was reported after the subject had been dosed. The treatment-related TEAE is defined as an adverse event that was assessed by the principal investigator as remotely, possibly, probably, or definitely related to the study drug.

The study protocol included subgroup analyses to explore the effects of the following covariates on the microbiologic cure rate of the two treatment groups: age, race, body mass index (BMI), number of *C. trachomatis* infections in the 12 months prior to enrollment, any STI in the 12 months prior to enrollment, and sexual activity.

Blood samples used for the determination of plasma rifalazil levels were collected from all subjects at visits 2, 3, and 4. These samples were to be analyzed for the subjects randomized to the rifalazil group if warranted by the study data after all subjects had completed the study and the blind was broken. The visit 2 and visit 3 drug plasma concentrations of the mITT subjects administered rifalazil were analyzed by liquid-liquid extraction and liquid chromatography-tandem mass spectrometry (LC-MS/MS) as described previously (15), with minor modifications, i.e., the instrument and column used. For this study, chromatographic separation was performed on the UltiMate 3000 LC system (Thermo Scientific, Waltham, MA) using a Kinetex C₁₈ column (100 by 2.1 mm) with a 2.6- μm particle size (Phenomenex, Torrance, CA), and a TSQ Quantum Ultra triple-quadrupole mass spectrometer (Thermo Scientific, Waltham, MA) was used for detection. Thermo Xcalibur software version 2.0 was used to operate the high-performance liquid chromatography (HPLC) and the mass spectrometer.

The clinical data were analyzed using SAS version 9.1 (SAS Institute Inc., Cary, NC), and adverse events were coded in MedDRA version 15. The plasma data were analyzed using Thermo Xcalibur software version 2.0 and R version 3.02.

RESULTS

Study population. The study was conducted from 9 July 2012 (first patient, first visit [FPFV]) to 9 April 2013 (last patient, last visit [LPLV]). In total, 84 subjects were screened (Fig. 1); 82 subjects were randomized to receive 25 mg of rifalazil (40 subjects) or 1 g of azithromycin (42 subjects), and there were two screening failures. The reason for the two screening failures was concurrent or prior intake of a contraindicated drug within 4 weeks of the study. Eighty-one (98.8%) subjects completed the study, 40 (100%) subjects in the rifalazil group and 41 (97.6%) subjects in the azithromycin group. Three subjects tested positive for both *C. trachomatis* and *N. gonorrhoeae* at baseline (overall rate of 3.7%; rifalazil, 2.5%, and azithromycin, 4.8%). One subject in the azithromycin group withdrew consent prior to visit 4 (day 36 to 40) before study completion. Eleven of the randomized subjects tested negative for *C. trachomatis* infection at baseline (7 in the rifalazil group and 4 in the azithromycin group), so the mITT population included 71 subjects (33 in the rifalazil group and 38 in the azithromycin group).

Table 1 summarizes the baseline subject characteristics of the ITT population and demonstrates that these attributes were balanced between treatment groups. The same trend was observed for the mITT population. Specifically, 52% of subjects in the mITT were African American (rifalazil, 51.5%; azithromycin, 52.6%) and 44% were Caucasian (rifalazil, 42.2%; azithromycin, 44.7%). The majority of subjects were non-Hispanic (rifalazil, 78.8%; azithromycin, 84.2%) and single (rifalazil, 87.9%; azithromycin, 89.5%). The median age (range) was 22.8 (19 to 35) years for subjects treated with rifalazil and 21.8 (19 to 39) years for subjects treated with azithromycin. The median (range) for body mass index (BMI) was 24.3 (17 to 51) kg/m² for rifalazil and 27.1

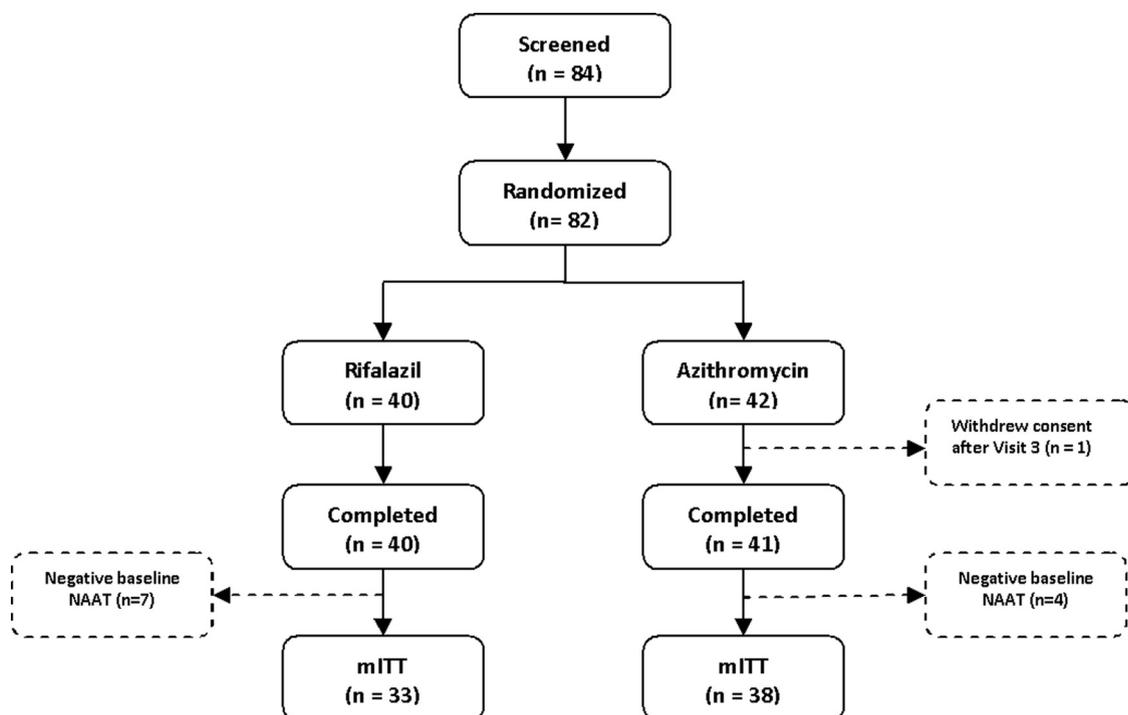


FIG 1 Disposition of subjects.

(18 to 59) kg/m² for azithromycin. One subject in the rifalazil group and two subjects in the azithromycin group had a positive *N. gonorrhoeae* test at baseline; these subjects received treatment with ceftriaxone. Eighty-two percent reported that they had no previous *C. trachomatis* infection (rifalazil, 81.8%; azithromycin, 81.6%) and 48% had no prior STI (rifalazil, 51.5%; azithromycin, 44.7%) in the 12 months prior to enrollment.

Efficacy results. The treatment efficacy results are shown in Table 2. Microbiological cure was achieved in 28 of 33 (84.8%) subjects in the rifalazil group and 35 of 38 (92.1%) subjects in the azithromycin group. The difference in microbiological cure rate was -7.3% (95% CI, -22.5 to 7.9). One subject who received rifalazil was considered a treatment failure at the test-of-cure visit per protocol-defined criteria due to an equivocal *C. trachomatis* NAAT result from testing at that visit, which when repeated was negative for *C. trachomatis*. Microbiological extended cure at visit 4 was achieved by 26 of 33 (78.8%) subjects in the rifalazil group and 31 of 38 (81.6%) subjects in the azithromycin group, even though the number of treatment failures at this visit in each group was the same. The difference in microbiological extended cure rate between the rifalazil and azithromycin group was -2.8% (95% CI, -21.7 to 16.1). Despite the small differences in the actual counts of microbiologic failure for the two groups, noninferiority was not established at visits 3 and 4 based on the protocol's prespecified margin.

The microbiological cure rates did not appear to differ between the two treatment groups in the subgroup analyses based on the baseline characteristics (i.e., age, race, BMI, and previous chlamydial or other sexually transmitted infections) and sexual activity reported between intake of medication and visit 3 (TOC).

Safety results. There were no withdrawals from the study due to adverse events, and there was one subject in the azithromycin

group with two non-treatment-related serious adverse events, pancreatitis and cholecystitis. The overall TEAE rates were 68% for rifalazil and 71% for azithromycin, while the treatment-related TEAE rates were 55% and 62%, respectively (Table 3). The most frequently reported treatment-related TEAE in the rifalazil group was an influenza-like illness in 5 (12.5%) subjects. For subjects in the azithromycin group, the most frequently reported treatment-related TEAEs were nausea in 14 (33.3%) subjects, diarrhea in 9 (21.4%) subjects, headache in 7 (16.7%) subjects, and bacterial vaginitis (i.e., bacterial vaginosis) in 5 (11.9%) subjects. The majority of TEAEs were of mild or moderate intensity. Grade 3 or 4 TEAEs were observed in 2 (5.0%) subjects in the rifalazil group (pyrexia, dehydration, and influenza) and in 6 (14.3%) subjects in the azithromycin group (gastroenteritis, bronchitis, vomiting, nausea, pancreatitis, cholecystitis, procedural pain, influenza, diarrhea, and nasopharyngitis). No clinically relevant trends or changes were apparent from the analyses of the actual laboratory and vital sign values and changes from baseline at visit 2 (on day 8 to 12).

Plasma concentrations of rifalazil. Rifalazil concentrations were quantifiable at visits 2 and 3 and were in the range of 0.54 to 3.1 ng/ml at visit 2 (on day 8 to 12) and 0.12 to 0.58 ng/ml at visit 3 (on day 22 to 26). The mean plasma concentration at visit 2 for the subjects who were treatment failures (1.4 ng/ml) appeared to be lower than that for treatment cures (1.7 ng/ml) (Fig. 2), but the difference was not significant ($P > 0.05$) using Welch's two sample *t* tests. The mean plasma concentrations at visit 3 were similar for both treatment cures (0.51 ng/ml) and failures (0.53 ng/ml). However, removing the subject with the equivocal result from the analysis resulted in the same trend as at visit 2, with a lower plasma rifalazil concentration for treatment failures than for those who were treatment cures.

TABLE 1 Baseline subject characteristics (ITT population)

Parameter	Value for subjects receiving:		Value for all subjects (<i>n</i> = 82)
	Rifalazil, 25 mg (<i>n</i> = 40)	Azithromycin, 1 g (<i>n</i> = 42)	
Age (yr)			
Mean (SD)	24.3 (4.76)	23.5 (4.51)	23.9 (4.62)
Median	23.7	22.0	22.7
Range	19–43	19–39	19–43
BMI (kg/m ²)			
Mean (SD)	27.4 (7.84)	28.4 (9.34)	27.9 (8.61)
Median	25.0	26.6	26.0
Range	17–51	18–59	17–59
Race [no. (%)]			
White	17 (42.5)	18 (42.9)	35 (42.7)
Black or African American	20 (50.0)	22 (52.4)	42 (51.2)
Asian	2 (5.0)	0 (0.0)	2 (2.4)
Other	1 (2.5)	2 (4.8)	3 (3.7)
Ethnicity [no. (%)]			
Hispanic or Latino	8 (20.0)	7 (16.7)	15 (18.3)
Not Hispanic or Latino	32 (80.0)	35 (83.3)	67 (81.7)
Marital status [no. (%)]			
Divorced	1 (2.5)	3 (7.1)	4 (4.9)
Married	3 (7.5)	1 (2.4)	4 (4.9)
Single	36 (90.0)	38 (90.5)	74 (90.2)
Baseline <i>N. gonorrhoeae</i> test result [no. (%)]			
Negative	39 (97.5)	40 (95.2)	79 (96.0)
Positive	1 (2.5)	2 (4.8)	3 (4.0)
Chlamydia episodes in preceding 1 yr [no. (%)]			
0	32 (80.0)	34 (81.0)	66 (80.5)
1	7 (17.5)	7 (16.7)	14 (17.1)
2	1 (2.5)	0 (0.0)	1 (1.2)
3	0 (0.0)	1 (2.4)	1 (1.2)
STIs in preceding 1 yr [no. (%)]			
0	20 (50.0)	19 (45.2)	39 (47.6)
1–2	17 (42.5)	17 (40.5)	34 (41.5)
3 or more (maximum of 12)	3 (7.5)	6 (14.3)	9 (11.0)

DISCUSSION

A proof-of-concept study to evaluate the safety and efficacy of a single dose of 25 mg of rifalazil in a phase 2 study in females with uncomplicated genital chlamydial infection was conducted following the promising results observed in the earlier phase 2 study in males with NGU (14).

The cure rate of 85% in the rifalazil group was similar to the cure rate reported by Stamm et al. from an earlier study in males administered a single dose of rifalazil for the empirical treatment of NGU (14). In that study, a single dose of 25 mg of rifalazil and a single dose

TABLE 2 Microbiologic cure at visit 3 and visit 4 (mITT population)

Visit, clinical response	Result for subjects receiving:		
	Rifalazil, 25 mg	Azithromycin, 1 g	Rifalazil–azithromycin
Visit 3			
Total no. of subjects	33	38	
No. (%) cured	28 (84.8)	35 (92.1)	(–7.3)
No. (%) failed	5 (15.2)	3 (7.9)	
95% CI	(72.4; 97.3)	(83.4; 100.0)	(–22.5; 7.9)
Visit 4			
Total no. of subjects	33	38	
No. (%) cured	26 (78.8)	31 (81.6)	(–2.8)
No. (%) failed	7 (21.2)	7 (18.4)	
95% CI	(64.6; 93.0)	(69.0; 94.1)	(–21.7; 16.1)

of 1 g of azithromycin had comparable clinical and microbiological cure rates (85% versus 83%) 2 weeks after the single-dose therapy (14); at 5 weeks postadministration, rifalazil had a higher microbiological cure rate (83%) than azithromycin (64%) (14).

This study was not powered, which is typical for phase 2b studies, but was considered adequate for a preliminary characterization of the efficacy and safety of rifalazil prior to designing a larger clinical investigation. A limitation of the current study was a higher number of baseline *C. trachomatis*-negative subjects in the rifalazil group (7 subjects) than in the azithromycin group (4 subjects), which made the mITT distribution uneven (*n* = 33 for rifalazil and *n* = 38 for azithromycin). In the current study, rifalazil did not demonstrate noninferiority to azithromycin at the visit 3 primary analysis; however, the number of treatment failures in each group, 5 and 3, respectively, was not markedly different. The number of failures at the secondary endpoint at visit 4 was similar (7 failures) in the rifalazil and azithromycin group. Despite the

TABLE 3 Treatment-related TEAE observed in more than 5% of subjects in any treatment group (ITT population)^a

Adverse event	No. (%) with indicated TEAE who received:	
	Rifalazil, 25 mg (<i>n</i> = 40)	Azithromycin, 1 g (<i>n</i> = 42)
At least 1 TEAE	22 (55.0)	26 (61.9)
Gastrointestinal disorders	10 (25.0)	22 (52.4)
Abdominal pain	2 (5.0)	4 (9.5)
Upper abdominal pain	0	3 (7.1)
Diarrhea	0	9 (21.4)
Nausea	3 (7.5)	14 (33.3)
Vomiting	4 (10.0)	3 (7.1)
General disorders and administration site conditions	11 (27.5)	1 (2.4)
Asthenia	3 (7.5)	0
Influenza-like illness	5 (12.5)	0
Pyrexia	3 (7.5)	0
Infections and infestations	9 (22.5)	8 (19.0)
Bacterial vaginitis	2 (5.0)	5 (11.9)
Nervous system disorders	4 (10.0)	7 (16.7)
Headache	3 (7.5)	7 (16.7)

^a Treatment-related treatment-emergent adverse events (TEAE) were coded using MedDRA version 15. Boldface indicates the system organ class (SOC) and the overall TEAE rates.

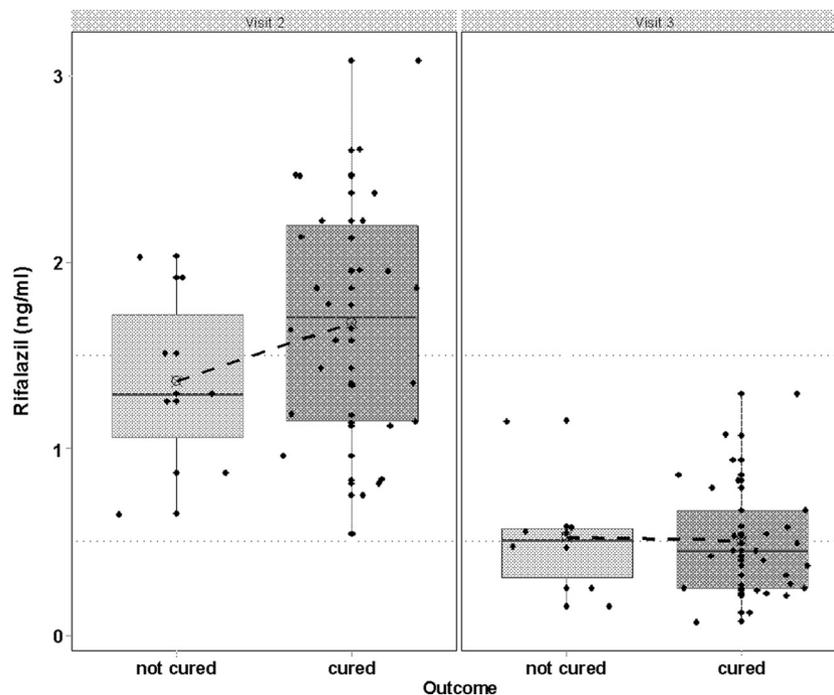


FIG 2 Rifalazil plasma concentration by cure or noncure. Box plot summaries of rifalazil plasma concentrations (dots) in women cured versus the concentrations in those not cured at visit 2 (day 8 to 12) (left) and visit 3 (day 22 to 26) (right). Box lines represent median values and interquartile ranges. Also shown are dashed lines connecting mean plasma concentrations (\otimes) of those cured and not cured at the respective visits.

same number of treatment failures in both groups, noninferiority was not established at visit 4 (secondary endpoint).

The overall rates of AE incidence (treatment emergent and treatment related) were comparable between the rifalazil group (68% and 55%) and the azithromycin group (71% and 62%). The most common adverse events with rifalazil were influenza-like illness and vomiting. These safety findings were consistent with previous studies of rifalazil, and those of azithromycin were consistent with what has been reported in the package insert, with the highest frequency of treatment-related AEs being related to the gastrointestinal system (nausea and diarrhea) (16).

The plasma concentrations of rifalazil at visits 2 and 3 were compared between subjects who failed the treatment and those who were cured. Rifalazil plasma concentrations were detectable after more than 3 weeks in all subjects after a single 25-mg dose of rifalazil, as expected based on rifalazil's previously reported long elimination half-life of ~ 100 h (11). Treatment failures at visit 2 (day 8 to 12) tended to have lower rifalazil plasma concentrations than those diagnosed as cured at the same visit; however, the difference was not significant. A similar trend was also observed at visit 3 (TOC), even with the inclusion of the subject with the equivocal result as a treatment cure.

The previous food effect study of rifalazil suggested that administration with a fatty meal decreases the pharmacokinetic variability of rifalazil (17). However, in this study, the consumption of the standard nutrition bar (approximately 30% fat) did not completely obviate the variability, as indicated by the variations in plasma concentrations for the cured and the treatment failure subjects. This suggests that there is room for an improved formulation of rifalazil that could provide more reliable drug absorption, as was reported by Chen et al. (17). This new formulation, in turn, may

reduce the intersubject variability and increase the efficacy of the study drug. However, other possible reasons for variability in plasma concentration, such as differences in hepatic metabolism and levels of rifalazil in the genital tract, have not been explored.

In conclusion, most chlamydia-infected women treated with single-dose rifalazil were cured and the drug was well tolerated. Rifalazil remains a promising single-dose alternative to azithromycin for the treatment of chlamydia, but an adequately powered study of rifalazil will be necessary to demonstrate that rifalazil is noninferior to azithromycin.

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