MAJOR ARTICLE

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A Randomized Study Evaluating Oral Fusidic Acid (CEM-102) in Combination With Oral Rifampin Compared With Standard-of-Care Antibiotics for Treatment of Prosthetic Joint Infections: A Newly Identified Drug–Drug Interaction

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Background. Fusidic acid (FA) has been used for decades for bone infection, including prosthetic joint infection (PJI), often in combination with rifampin (RIF). An FA/RIF pharmacokinetic interaction has not previously been described.

Methods. In a phase 2 open-label randomized study, we evaluated oral FA/RIF vs standard-of-care (SOC) intravenous antibiotics for treatment of hip or knee PJI. Outcome assessment occurred at reimplantation (week 12) for subjects with 2-stage exchange, and after 3 or 6 months of treatment for subjects with hip or knee debride and retain strategies, respectively.

Results. Fourteen subjects were randomized 1:1 to FA/RIF or SOC. Pharmacokinetic profiles were obtained for 6 subjects randomized to FA/RIF. FA concentrations were lower than anticipated in all subjects during the first week of therapy, and at weeks 4 and 6, blood levels continued to decline. By week 6, FA exposures were 40%–45% lower than expected.

Conclusions. The sponsor elected to terminate this study due to a clearly illustrated drug–drug interaction between FA and RIF, which lowered FA levels to a degree that could influence subject outcomes. Optimization of FA exposure if used in combination with RIF should be a topic of future research.

Clinical Trials Registration. NCT01756924.

Keywords. prosthetic joint infection; arthroplasty; fusidic acid; rifampin.

Joint replacement surgery has become increasingly common, and as the population ages, the burden of prosthetic joint infection (PJI) is projected to increase. CEM-102 (sodium fusidate, fusidic acid), hereafter referred to as FA, is the only marketed member of a novel class of natural product antibiotic, the fusidanes, initially identified from *Fusidium coccineum* in 1960 [1]. Fusidic acid binds with the ribosomal translocase, elongation factor G (EF-G), preventing the dissociation of the EF-G-DP complex from the ribosome, inhibiting protein synthesis and bacterial growth [2–4]. Oral and topical FA have been used in various countries in Western Europe for >4 decades to treat staphylococcal infections.

FA has potent in vitro activity against gram-positive aerobic organisms. Antimicrobial activity against staphylococci recovered from US subjects with blood, bone and joint, respiratory tract, and skin infections as part of a surveillance study conducted in 2014 showed that FA inhibited 99.8% of 1804 *Staphylococcus aureus* isolates (and 100.0% of 848 methicillin-resistant *S. aureus* [MRSA] isolates) at a minimum inhibitory concentration (MIC) ≤ 1 μg/mL (minimum inhibitory concentration for which 90% of isolates inhibited [MIC_{90}] = 0.12 μg/mL for both) [5]. The majority of coagulase-negative staphylococci were similarly susceptible (MIC_{90} = 0.25 μg/mL). Among other gram-positive bacteria, FA has activity against enterococci (MIC_{90} = 4 mg/L) [6], *Corynebacterium* species (MIC ≤ 0.12 μg/mL) [7], *Micrococcus luteus* (MIC ≤ 0.5 μg/mL) [7], *Streptococcus pyogenes* (MIC_{90} = 8 μg/mL) [6], and *Propionibacterium* species (MIC_{90} = 1 μg/mL) [8].

Rifampin (RIF) has emerged as a valuable antibiotic in the treatment of PJIs, due to its unique activity in the setting of bacterial biofilms. In a landmark study, Zimmerli and colleagues [9] demonstrated the role of RIF in the effective treatment of PJI when used in combination with initial intravenous therapy and follow-on oral antibiotic therapy. However, RIF cannot be used as monotherapy due to the high rate of resistance emergence

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when used alone [10]. FA has also demonstrated activity against *S. aureus* biofilms in vitro, both as a single agent and in combination with daptomycin, vancomycin, or linezolid [11].

The combination of FA and RIF to treat PJIs has demonstrated efficacy and safety [12, 13], at doses similar to those used in this study. To date, however, there have been no pharmacokinetic (PK) reports of FA and RIF given in combination, either from a healthy volunteer drug–drug interaction (DDI) study or from patients receiving combination therapy. The purpose of this phase 2 trial was to assess the safety, tolerability, efficacy, and PK of oral FA and RIF when used in combination compared with intravenous standard-of-care (SOC) antibiotic therapy, for the treatment of hip or knee PJI or spacer infection.

METHODS

Study Design

This was a phase 2, open-label, multicenter, randomized study to evaluate oral FA plus RIF compared to SOC antibiotics for the treatment of PJI (hip or knee) or spacer infections, in subjects managed by 2-stage surgical exchange or debridement and retention (DAR) strategies. One hundred subjects were to be enrolled with the goal of randomizing 50 subjects (25 subjects per treatment arm). PK blood sampling was performed for subjects randomized to FA/RIF.

A randomized discontinuation study design allowing assessment of FA/RIF tolerability prior to randomization was utilized (Supplementary Figure 1). Enrolled subjects received loading doses of FA and RIF in addition to intravenous SOC antibiotic therapy initiated at the time of explant surgery or DAR. Subjects meeting criteria for randomization (FA/RIF tolerability and positive microbiological assessment) were randomized 1:1 to either the FA/RIF or SOC arm.

Intraoperative cultures were obtained at the time of debridement or explant surgery and at the time of prosthesis reimplantation. Treatment continued for 6 weeks in subjects managed by 2-stage surgical exchange, and 3 or 6 months for hip or knee DAR, respectively. Clinical outcome was assessed on the day of reimplantation surgery (around week 12) for subjects managed with 2-stage exchange and, for subjects with hip or knee infection managed with DAR, at the end of scheduled treatment, which was 3 or 6 months, respectively.

Study Population

Adults ≥18 years of age with prosthetic knee or hip joint or spacer infection, with recent or planned surgery (2-stage exchange or DAR surgery), and suitable for oral antibiotic therapy were enrolled. For randomization, all isolated gram-positive organisms must have been susceptible to FA, and all staphylococcal isolates must have also demonstrated susceptibility to RIF. Isolation of gram-negative bacteria or fungi was exclusionary.

Antibacterial Treatment

All subjects had received SOC intravenous antibiotics at the time of randomization. Subjects were randomized 1:1 to either oral FA plus RIF or SOC intravenous antibiotics, in accordance with the Infectious Diseases Society of America clinical practice guidelines for PJI [14] and local standard practice. FA was administered orally as 2 loading doses of 1500 mg 12 hours apart on day 1, followed by 900 mg twice daily thereafter. The FA maintenance dose was later lowered to 900 mg in the morning and 600 mg in the evening or vice versa (1500 mg total daily dose) to improve tolerability, and temporary FA dose reduction to 600 mg twice daily in response to poor tolerability was permitted. RIF was administered orally as 450 mg twice daily. Dose reduction to 300 mg twice daily for subjects weighing <80 kg, with estimated creatinine clearance of 30–50 mL/minute, with poor tolerability, or at the investigator's discretion, was permitted. Treatment continued for 6 weeks in subjects managed by 2-stage surgical exchange, and 3 or 6 months for hip or knee DAR, respectively. Chronic suppressive therapy was allowed thereafter.

Pharmacokinetic Evaluations

Plasma for FA/RIF PK was collected on 3 days: approximately day 7, and at weeks 4 and 6. Samples were drawn prior to dosing, at 1, 2, and 4 hours postdose and 6–8 hours postdose. Plasma concentrations of FA and of RIF and its metabolite, 25-desacetyl rifampin, were determined using sensitive and selective, validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) methods. Assays were performed by Microconstants, Inc (San Diego, California). Where feasible, plasma concentration-time data were analyzed by noncompartmental analysis using Phoenix/WinNonlin version 6.3 (PharSight Corporation, Mountain View, California).

Clinical Response

The primary outcome (clinical success, clinical failure, or indeterminate status) was determined by the investigator at the test-of-cure (TOC) visit. Clinical success was defined as no evidence of infection, by cultures obtained at prosthesis reimplantation, arthrocentesis, arthroscopy, or arthrotomy, in a subject whose antibiotic therapy was not changed (other than dose adjustments). The TOC assessment occurred at reimplantation (around week 12) for subjects with a 2-stage exchange, and after 3 or 6 months of treatment for subjects with a hip or knee DAR, respectively.

RESULTS

Demographics and Subject Disposition

A total of 41 subjects were enrolled between April 2013 and April 2014. Twelve subjects were enrolled but not dosed (did not meet protocol criteria for study drug dosing); 15 subjects were enrolled, dosed, but not randomized; and 14 subjects were enrolled, dosed, and randomized (7 to FA/RIF and 7 to SOC) (Supplementary Figure 2). Baseline characteristics for the 14 enrolled, dosed, and randomized subjects (safety–intent-to-treat population) are presented in Table 1.

Table 1. Baseline Characteristics for Safety-Intent-to-Treat Population and Outcome

Subject ID	Age, y	Sex	Site of PJI Infection	Surgical Procedure	Baseline Inclusionary Pathogen	Baseline FA/RIF MIC, μg/mL	Randomized Therapy	Outcome	Reason for Failure
103-01	62	M	Hip	2-stage exchange	MSSA	0.12/0.03	FA/RIF	Success	
103-02	64	M	Hip	DAR	MRSA	0.12/0.015	FA/RIF	Failure	AE; switched to new antibiotic
108-07	75	M	Knee	2-stage exchange	Culture negative	NA	FA/RIF	Failure	Persistent inflammation
111-01	66	F	Knee	2-stage exchange	*Staphylococcus epidermidis*	0.25/0.015	FA/RIF	Success	
112-04	64	F	Knee	2-stage exchange	No inclusionary pathogens	NA	FA/RIF	Success	
114-03	86	F	Knee	2-stage exchange	MSSA	0.12/0.015	FA/RIF	Success	
114-06	72	M	Knee	2-stage exchange	MRSA	0.12/0.25	FA/RIF	Failure	Infection recurrence (MRSA resistant to RIF)
103-03	45	M	Hip & spacer	DAR & spacer replacement	MRSA	. . .	SOC	Indeterminate	Insufficient data; study discontinued
104-08	62	M	Knee	2-stage exchange	*S. epidermidis*	. . .	SOC	Success	
108-04	65	M	Knee	2-stage exchange	*S. epidermidis*	. . .	SOC	Failure	AE; switched to new antibiotic
108-06	83	M	Knee	2-stage exchange	Group B streptococci	. . .	SOC	Success	
108-08	64	F	Hip	2-stage exchange	Culture negative	. . .	SOC	Indeterminate	Insufficient data; study discontinued
114-05	61	M	Knee	2-stage exchange	*S. epidermidis*	. . .	SOC	Success	
114-07	77	F	Hip & spacer	2-stage exchange	MSSA	. . .	SOC	Success	

Abbreviations: AE, adverse event; DAR, debridement and retention; FA, fusidic acid; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NA, not applicable; PJI, prosthetic joint infection; RIF, rifampin; SOC, standard of care.

Four randomized subjects (n = 2 [28.6%] from each arm) prematurely withdrew from the study before TOC (Table 2), 2 subjects on the SOC arm due to early termination of the study by the sponsor. One subject (n = 1 [14.3%]) randomized to SOC prematurely discontinued SOC study drug due to an adverse event (AE) (vancomycin-associated fever), and 1 subject (n = 1 [14.3%]) randomized to FA/RIF prematurely discontinued study drug due to AEs of nausea and diarrhea.

Table 2. Subject Disposition for Safety–Intent-to-Treat Population

Subject Disposition	FA/RIF, No. (%)	SOC, No. (%)
Safety-ITT population (randomized subjects who received at least 1 dose of study drug)	7	7
Subjects who completed study	3 (42.9)	1 (14.3)
Subjects prematurely withdrawing from study prior to TOC	2 (28.6)	2 (28.6)
Reason for premature withdrawal		
Noncompliance with protocol-required procedures	1 (14.3)	0 (0.0)
Sponsor decision	1 (14.3)	1 (14.3)
Other	0 (0.0)	1 (14.3)
Subjects who completed study drug	5 (71.4)	6 (85.7)
Subjects prematurely discontinuing study drug	2 (28.6)	1 (14.3)
Reason for premature discontinuation from study drug		
Adverse event	1 (14.3)	1 (14.3)
Development of a clinically significant laboratory abnormality	1 (14.3)	0 (0.0)

Abbreviations: FA, fusidic acid; ITT, intent to treat; RIF, rifampin; SOC, standard of care; TOC, test of cure.

Efficacy Results

Due to early study closure, the availability of efficacy data are limited. Of 7 subjects enrolled in each treatment arm, therapy was considered successful at the TOC visit in 4 subjects in each arm (Table 1). However, 2 of the FA/RIF subjects were culture negative at enrollment (therapy was considered successful for 1), and 2 of the SOC subjects did not reach TOC due to early study closure; therefore, final determination of their outcome is not possible, even though they might have ultimately been successes.

Of particular interest, 1 subject in the FA/RIF group with MRSA (subject 114-06) demonstrated microbiological treatment failure. For that subject, the MRSA strain isolated at the initial explant surgery was susceptible to both FA (MIC = 0.12 μg/mL) and RIF (MIC = 0.25 μg/mL). On the day of reimplantation surgery (day 105), a MRSA strain resistant to RIF (MIC = 8 μg/mL) was recovered from 2 tissue biopsies, but the isolates remained susceptible to FA (MIC = 0.06 μg/mL). This microbiological failure was potentially related to depressed FA levels due to a DDI (described below), resulting in essentially RIF monotherapy. This subject (114-06) had the lowest FA plasma concentrations of all the subjects at week 1 (taking 1800 mg FA total daily dose) and at week 4 (taking 1500 mg FA total daily dose) (Figure 1).

Safety Results

Similar to efficacy, due to early study closure, the safety database is limited. Gastrointestinal disorders of mild or moderate

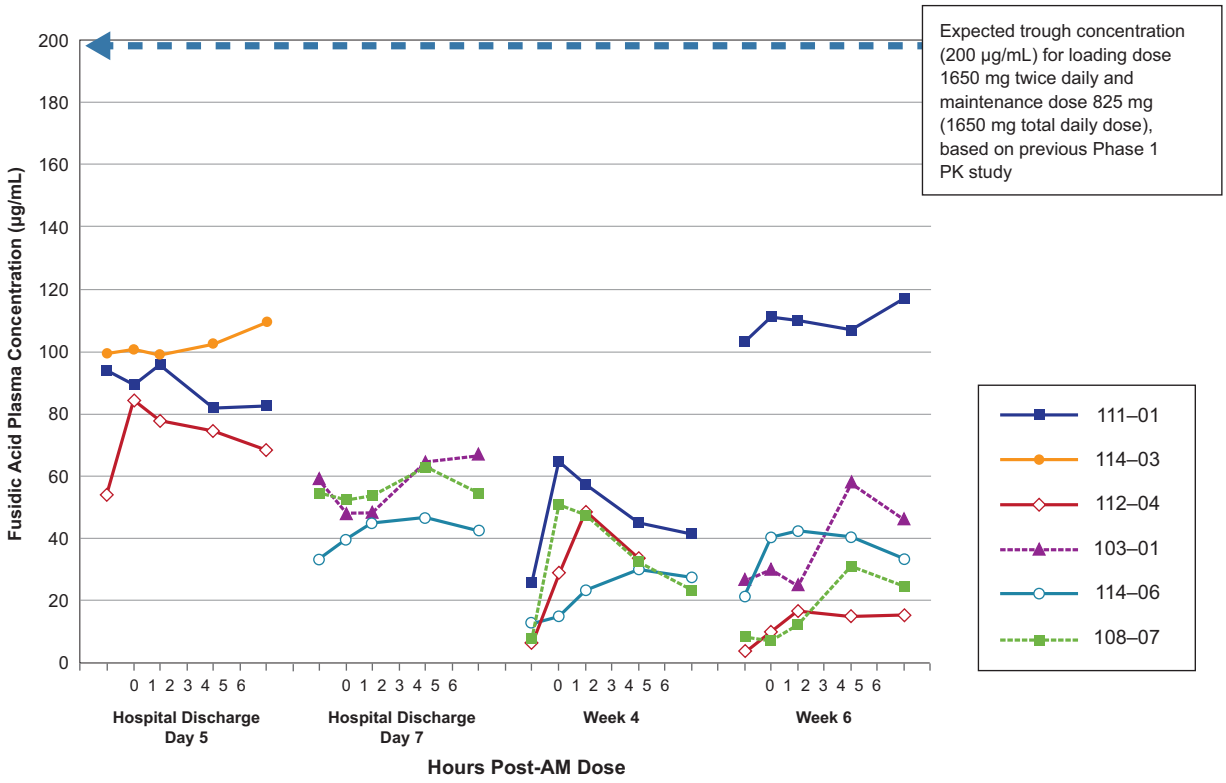

Figure 1. By subject (hours post-AM dose) fusidic acid plasma concentrations. Subject 111-01 discontinued rifampin at week 4 due to intolerance. Actual plasma concentrations are plotted. Abbreviation: PK, pharmacokinetic.

intensity were reported most frequently by both treatment groups, the most common being nausea and diarrhea.

Pharmacokinetic Results

Pharmacokinetic data for 6 of 7 FA/RIF-treated subjects were obtained and a summary of the dosing prior to each PK day is shown in Table 3. Concentration-time data were analyzed using noncompartmental approaches as implemented in WinNonLin Phoenix (Certara). Because FA dose reductions to 600 mg twice daily were permitted, PK parameters were dose-normalized using the subject's dose the week prior to the PK assessment, and dose-normalized parameters were used to determine the change in exposure from week 1 at weeks 4 and 6. The mean FA (dose normalized) percentage decrease in area under the concentration-time curve (AUC) was 43% at week 4 and 45% at week 6 (Figure 2). One subject (subject 111-01) did not receive RIF after week 4, so week 6 data were excluded from PK analysis of a potential DDI.

The mean RIF maximum plasma concentration (C_{max}) on week 4 was approximately 34% lower than week 1, while the week 6 C_{max} was approximately 42% lower than week 1. The mean RIF AUC on week 4 was approximately 45% lower than week 1, while the week 6 AUC was approximately 47% lower than week 1 (not shown).

Based on a prior phase 1 PK study with FA (using a loading dose of 1650 mg twice daily and maintenance dose of 825 mg twice daily), the expected steady-state trough concentrations were 200 µg/mL [15]. As shown in Figure 1, FA concentrations were lower than anticipated in all subjects during the first week of therapy and, at weeks 4 and 6, FA blood levels continued to decline. By week 6, FA exposures were 40%–45% lower than previously observed exposures with similar dosing regimens, suggesting a substantial DDI in which RIF lowers FA concentrations.

Table 3. Summary of Study Drug Administration in Subjects Randomized to Fusidic Acid/Rifampin

	FA Total Daily Dose, mg			RIF Total Daily Dose, mg		
Subject	Hospital Discharge	Week 4	Week 6	Hospital Discharge	Week 4	Week 6
111-01	1800	1200	1200	900	300	0
114-03	1800	1200	1500	600	600	600
103-01	1800	1800	1800	900	900	900
114-06	1800	1500	1500	900	900	900
108-07	1200	1200	1500	600	600	600
112-04	1500	1500	1200	900	900	900

Abbreviations: FA, fusidic acid; RIF, rifampin.

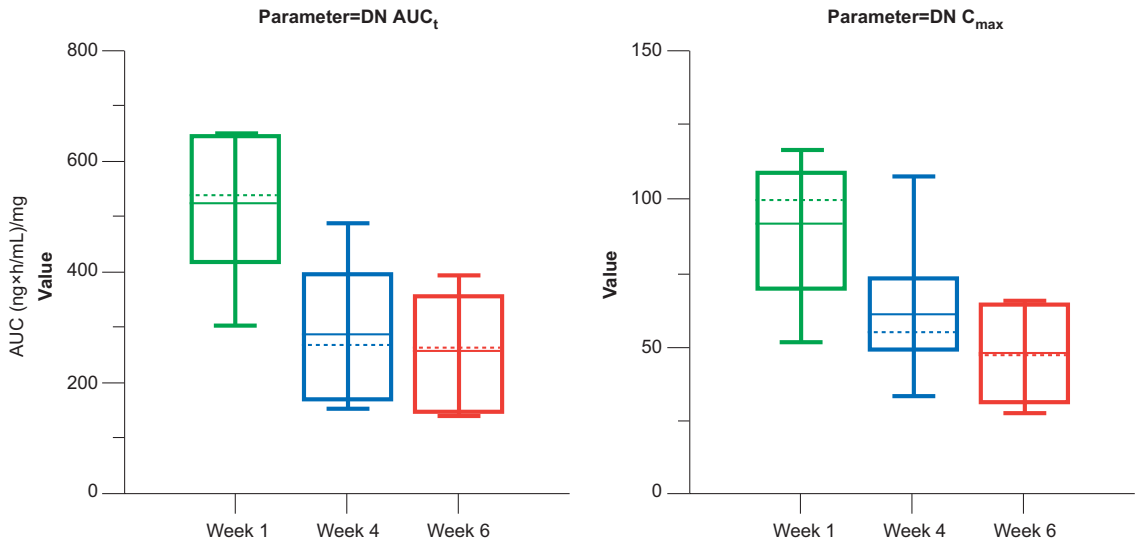

Figure 2. Box-and-whisker plot of dose-normalized (DN) area under the concentration-time curve from time zero to last measurable concentration-time point (AUC_t) and maximum plasma concentration (C_{max}) of fusidic acid, by week. Outliers of the distributions are not shown. Subject 111-01 at week 6 was not included in this analysis because this subject did not receive rifampin after week 4, and data do not contribute to the evaluation of the drug–drug interaction.

The observation of a DDI is clearly illustrated in the FA plasma concentrations of subject 111-01 (Figure 1). At the time of hospital discharge on day 5, this subject had an FA C_{max} of 95.6 μg/mL and $AUC_{(0-t)}$ of 581 μg × h/mL, having received FA 1800 mg total daily dose (TDD) and RIF 900 mg TDD. Following hospital discharge, a dose adjustment to FA 1200 mg TDD and RIF 300 mg TDD was made to manage gastrointestinal intolerance. At week 4, the FA C_{max} and $AUC_{(0-t)}$ had decreased substantially, to 64.6 μg/mL and 292 μg × h/mL, respectively. At this visit, RIF was discontinued due to elevated bilirubin and the subject continued on FA monotherapy. By week 6, when the subject was only taking FA 1200 mg TDD, the FA plasma concentration levels markedly increased, to a C_{max} and $AUC_{(0-t)}$ of 117 μg/mL and 658 μg × h/mL, respectively. This C_{max} was more consistent with steady-state plasma concentrations observed with a similar dosing regimen in the phase 1 PK study [15]. Antimicrobial therapy was successful in this subject.

DISCUSSION

When coadministered with RIF, a decline in FA plasma levels occurred by day 5–7 and worsened through weeks 4 and 6. These levels were lower than the expected steady-state trough concentrations based on phase 1 PK data. The likely mechanistic explanation for the interaction is induction of cytochrome P450 3A4 (CYP3A4) by RIF. As FA is metabolized primarily by CYP3A4, coadministration results in more rapid metabolism of FA. Not illustrated in this article, as it has been well described in the literature, a decline in RIF plasma levels over time was also observed in our study, and is likely due to autoinduction of metabolism [16]. Although the interaction between FA and RIF may seem predictable, clinical practice over the past decade has supported use of this antibiotic combination [12, 13, 17].

When coadministered, a reduction in FA exposure creates an opportunity for rapid emergence of RIF resistance and subsequent treatment failure. This may have occurred in 1 subject assigned to the FA/RIF group; MRSA initially recovered during explant surgery was susceptible to both FA and RIF. On day 105 at reimplantation surgery, MRSA, now resistant to RIF with an MIC of 8 μg/mL (however, still susceptible to FA), was again recovered. This single case mirrors the experience of Drancourt [13], in which FA/RIF was as effective as ofloxacin/RIF; however, treatment failures were typically associated with emergent staphylococcal RIF resistance, but not FA resistance. Treatment guidelines for PJI include the recommendation for RIF along with a second antibiotic [14]. Specifically, the practice of using RIF plus FA is supported by data from 1 randomized controlled trial [13] and 2 retrospective studies [12, 18]. However, it should be noted that aggressive surgical debridement and intravenous antibiotics to reduce the bacterial burden prior to long-term oral antibiotic therapy likely contributed to the high clinical success rate (90%) observed in the Aboltins study [12]; and the importance of these interventions should not be understated. Furthermore, as discussed in this article, the combination of FA with RIF presents PK challenges.

To summarize, the sponsor elected to terminate this study due to a clearly illustrated DDI between FA and RIF, which lowered FA levels to a degree that could influence subject outcomes. The combination of FA and RIF has been used for the treatment of PJI in many parts of the world for decades; however, based on these PK data, optimization of FA exposure if used in combination with RIF should be a topic of future research.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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Potential conflicts of interest. R. P., K. K., C. M., D. O., and P. F. are employees of Cempra Inc. M. D. I.-U. is a former employee of Cempra Inc. D. R. M. is a paid consultant for Cempra Inc. R. D. and R. B. have received research grants from Cempra Inc. S. K. has received royalties from Corin and Stryker, and stock options from Innovative Technologies. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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