Rifampin (RIF) significantly reduces plasma concentrations of fusidic acid (FA) when used in combination for treatment of prosthetic joint infection (PJI)

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INTRODUCTION AND PURPOSE

With the increasing number of surgeries for joint replacement, the need for addressing prosthetic joint infections (also known as PJIs) is of increasing importance. In the US, it is estimated that the incidence of PJIs is nearly 20,000/year, with an infection rate of about 1-2% [**1**].

Although not approved for use in the US, fusidic acid, also known as CEM-102, is being developed in the US for the treatment of bone and joint infections (BJI) due to its spectrum of activity, ability to penetrate into bone at therapeutic concentrations **[2, 3]**, and long history ex-US of safe use in chronic therapy [**4**].

Fusidic acid, derived from the fungus *Fusidium coccineum*, is a member of the fusidane class of antibiotics. It acts by inhibiting bacterial protein synthesis, by binding to elongation factor G (EF-G). Fusidic acid has shown potent activity against the majority of gram-positive pathogens associated with PJIs such as coagulase negative staphylococci, both methicillin resistant and sensitive *Staphylococcus aureus* and *Corynebacterium* [**5**]. Fusidic acid has also demonstrated activity against *Propionibacterium acnes* [**6**] as well as *Clostridium, Enterococcus* and *Streptococcus* spp. [**7**].

Fusidic acid has been used for over three decades in both Europe and Australia for the treatment of bone and joint infections (BJIs), and skin and soft tissue infections [**8**]. It has been widely used in combination with rifampin during therapy. RIF is favored by bone and joint specialists for use in BJI due to its ability to penetrate and disperse biofilms. However, rifampin cannot be used in monotherapy due to the high rate of resistance that emerges when it is used without a second antibiotic [**9**]. Several studies have been conducted using fusidic acid in combination with rifampin (RIF) to treat PJIs [**10, 11, 12**]. In each of these studies, such combination therapy demonstrated both efficacy and clinical success. To date, there have been no reports of the pharmacokinetics of either FA or RIF during combination therapy.

The purpose of this Phase 2 trial was to assess the safety, tolerability, and efficacy of oral fusidic acid/rifampin in comparison with intravenous standard-of-care (IV-SOC) antibiotic therapy, for the treatment of hip or knee PJI or spacer infection following surgery. As part of the study, FA and RIF pharmacokinetics were also evaluated.

MATERIALS AND METHODS

This was a Phase 2, open-label, multi-center, randomized study in patients with hip or knee PJI or spacer infection following surgery. Surgical intervention included either a 2-stage exchange strategy or debridement and prosthesis retention. Following surgery, patients were started on IV antibiotic therapy. Fusidic acid and rifampin pharmacokinetics were also evaluated.

Intraoperative samples for bacterial culture were obtained initially to diagnose PJI (at the time of debridement or infected prosthesis explant surgery) and at the time of new prosthesis implantation, in subjects managed by two-stage surgery. Isolate species confirmation and susceptibility testing were performed at a Reference Microbiology Laboratory (JMI Laboratories, North Liberty, Iowa).

Fusidic acid (CEM-102) was administered orally with a loading dose of 1500 mg twice daily (BID) or 3000 mg total daily dose (TDD) on Study Day 1, followed by 1500 mg TDD (900 mg in the morning and 600 mg in the evening, or vice versa) thereafter. Temporary CEM-102 dose reduction to a 1200 mg TDD (or 600 mg BID) in response to poor tolerability (symptoms or safety laboratory abnormalities) of therapy was permitted before or after randomization.

Rifampin was administered orally at a dose of 450 mg BID (TDD 900 mg). Dose reduction to 300 mg BID (TDD 600 mg) for subjects <80 kg, for subjects with estimated creatinine clearance (CrCl) of 30 to 50 mL/min, in response to poor tolerability (i.e. nausea or other GI side effects), or at the Investigator's discretion was permitted before or after randomization.

Disclosures: This clinical trial was sponsored by Cempra, Inc.

RESULTS

A total of 41 subjects were enrolled, 15 were dosed but not randomized, 7 were randomized to CEM-102/RIF, and 7 were randomized to SOC.

Prior to reaching the projected enrollment of 100 subjects, the study was terminated in July 2014, due to a significant drug-drug interaction between fusidic acid and rifampin. The pharmacokinetic profiles for six of the seven patients randomized to fusidic acid/rifampin were obtained and a summary of the dosing regimen the subjects received prior to each PK visit day are shown in **Table 1.**

Table 1: Summary of Study Drug Administration in Subjects Randomized to Fusidic Acid/Rifampin

Subject	Fusidic Acid TDD (mg)			Rifampin TDD (mg)		
	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

Based on a prior Phase 1 PK trial with fusidic acid (which utilized either a loading dose of 2200 mg and maintenance dose of 1100 mg or 3300 mg loading dose and 1650 mg maintenance dose), the expected steady state trough concentrations were 100 or 200 µg/mL, respectively [**13**]. As shown in **Figure 1**, during the first week of therapy, all subjects had fusidic acid concentrations lower than anticipated. At week 4 and week 6, blood levels continued to decline. By week 6, fusidic acid exposures were 50-80% lower than the previously observed exposures with similar dosing regimens suggesting a substantial drug-drug interaction whereby rifampin lowers fusidic acid concentrations.

The observation of a drug-drug interaction is clearly illustrated in the plasma concentrations of subject 111-01 **(Table 2).** At the time of hospital discharge on Day 5, this patient had a C_{max} of 95.6 µg/mL and $AUC_{(0-t)}$ of 581 µg·h/mL, having received 1800 mg TDD of fusidic acid and 900 mg TDD of rifampin. Following hospital discharge, a dose adjustment to fusidic acid TDD of 1200 mg and rifampin TDD of 300 was made to manage GI tolerance. At the week 4 visit, this patient's C_{max} and $AUC_{(0-t)}$ had decreased substantially, to 64.6 µg/mL and 292 µg·h/mL, respectively. At this visit rifampin was discontinued due to elevated bilirubin and the subject continued on fusidic acid monotherapy. By Week 6, when the subject was only taking fusidic acid at a TDD of 1200 mg, the fusidic acid plasma concentration levels markedly increased. Specifically, the C_{max} and AUC (0-t) were 117 µg/mL and 658 µg·h/mL, respectively. This C_{max} was in line with the steady state plasma concentrations observed with a similar dosing regimen in the Phase 1 PK trial [**13**]. Antimicrobial therapy was successful in this patient.

True microbiological failure was observed in one subject (114-06). Prior to fusidic acid/rifampin therapy, a methicillin-resistant *Staphylococcus aureus* was recovered from a tissue biopsy taken during explant surgery. The isolate was susceptible to both study drugs, with an MIC of 0.12 µg/mL for fusidic acid and an MIC of 0.25 µg/mL for rifampin. On the day of re-implantation surgery (Day 105), MRSA, resistant to rifampin with MIC of 8 µg/mL, was recovered from two tissue biopsies. However, the isolates remained susceptible to fusidic acid.

Figure 1: Fusidic Acid Plasma Concentrations

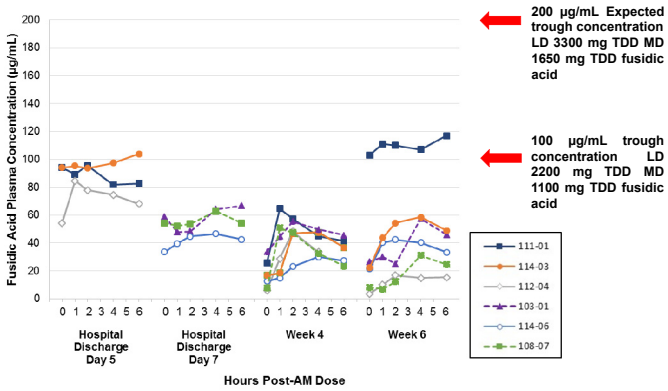

Table 2: Pharmacokinetic Parameters for Subject 111-01 following Fusidic Acid Dosing

Visit	Fusidic Acid TDD (mg)	Rifampin TDD (mg)	C_{max} (µg/mL)	T_{max} (h)	$AUC_{(0-t)}$ (µg·h/mL)	DN* C_{max} (µg/mL)/mg	DN* AUC_t (µg·h/mL)/mg
Day 5	1800	900	95.6	2.45	581	0.106	0.646
Week 4	900	300	64.6	1.17	292	0.108	0.487
Week 6	900	0	117	6	658	0.195	1.100

DN* = Dose Normalized. With dose adjustments throughout the study, comparison of PK parameters from week to week was made by dose normalizing the C_{max} and AUC for all analytes

CONCLUSIONS

Although recommended therapies for PJI include the combination of rifampin and a second oral antimicrobial agent, it was determined from this study that the fusidic acid/rifampin combination resulted in a significant drug-drug interaction. This interaction caused a substantial decline in fusidic acid plasma levels, which occurred by Day 5-7 and worsened through Day 28 (Week 4) and Day 42 (Week 6). These levels were much lower than the expected steady state trough concentrations of 100 or 200 µg/mL, based on Phase 1 PK trial data.

For one of the patients, 111-01, who had stopped taking rifampin after Week 4, there was a substantial rebound in fusidic acid levels observed at the Week 6 visit. The results from this study suggest that rifampin substantially reduces fusidic acid exposures, thereby creating an opportunity for emergent rifampin resistance and subsequent treatment failure. This was observed in one patient in this trial.

The results of this trial demonstrate that fusidic acid and rifampin should not be used in combination therapy due to a significant drug-drug interaction that decreases fusidic acid exposures by 50-80%, essentially resulting in rifampin monotherapy. Therefore, the use of fusidic acid/rifampin combination therapy for the treatment of PJI should be reevaluated.

Fusidic acid remains an effective antibiotic for the treatment of skin, bone, and joint infections and will soon be evaluated in monotherapy in a Phase 3 trial for the treatment of refractory staphylococcal bone or joint infections in patients for whom curative surgery is not a reasonable option.

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