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A Randomized Double-Blind Placebo-Controlled Dose-Escalation Phase 1 Study of Aerosolized Amikacin and Fosfomycin Delivered via the PARI Investigational eFlow® Inline Nebulizer System in Mechanically Ventilated Patients

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Abstract

Background: This clinical trial evaluated the pharmacokinetics and safety/tolerability of amikacin/fosfomycin solution using a vibrating plate nebulizer, in mechanically ventilated patients with ventilator-associated tracheobronchitis (VAT) or ventilator-associated pneumonia (VAP).
Methods: Nine adult patients were consented to receive three escalating doses of a combination of 50 mg/mL amikacin and 20 mg/mL fosfomycin; doses were separated by 24 ± 2 hr. On day 3, patients received two blinded, randomized treatments (amikacin/fosfomycin and volume-matched placebo), separated by 2 hr. All treatments were administered with a single-patient, multitreatment nebulizer (Investigational eFlow® Inline Nebulizer System; PARI Pharma GmbH, positioned in the inspiratory limb tubing between the ventilator and the patient. The nebulizer remained in-line until all treatments had been delivered. Concentrations of amikacin and fosfomycin were measured in tracheal aspirate and plasma samples obtained during the 24 hr after each dose.
Results: Fifteen minutes after dosing with the 300/120 mg amikacin/fosfomycin combination, tracheal aspirate amikacin concentrations ± SD were 12,390 ± 3,986 μg/g, and fosfomycin concentrations were 6,174 ± 2,548 μg/g (n=6). Airway clearance was rapid. Plasma concentrations were subtherapeutic; the highest observed amikacin plasma concentration was 1.4 μg/mL, and the highest observed fosfomycin plasma concentration was 0.8 μg/mL. Administration time was approximately 2 min/mL. No adverse effects on respiratory rate, peak airway pressures, or oxygenation were observed during or following drug or placebo administration.
Conclusions: High tracheal aspirate concentrations of amikacin and fosfomycin were achieved in mechanically ventilated patients with VAT or VAP after aerosolized administration with an inline nebulizer system. Airway clearance was rapid. No adverse respiratory effects were noted during or following drug administration.

Key words: amikacin, fosfomycin, aerosol delivery, ventilator, ventilator-associated pneumonia

Introduction

Aerosolized Antibiotics have become the standard of care in cystic fibrosis patients with chronic endobronchial pseudomonal infections.[1,2] Adjunctive aerosol antibiotic therapy to treat Gram-negative pneumonia in patients on mechanical ventilation has been studied for over 30 years with encouraging results; however, multicenter, placebo-controlled, randomized trials are needed to establish which antibiotics and drug delivery systems are most efficacious.[3–8]

The emergence of highly resistant Gram-negative bacteria has increased the amount of aminoglycoside required for a

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potentially effective dose.[9] In a recent survey of 35,000 hospital isolates, the highest amikacin minimum inhibitory concentration (MIC) for Gram-negative bacteria was greater than 1,024 μg/mL.[10] Due to sputum antagonism, the target concentration of an aminoglycoside needed for bactericidal activity is 25-fold the MIC.[11,12]

Drug delivery issues include particle size and lung deposition. Hygroscopic growth from the humidified air in the ventilator circuit can increase the mean droplet size, leading to rainout in the endotracheal tube and poor delivery to the lower airways.[3,13] The airflow from a continuously run jet nebulizer can create a high bias flow that flushes most of the aerosol into the expiratory limb of the ventilator during exhalation by the patient.[3,13] A novel approach to the drug delivery issues was to develop a vibrating plate nebulizer positioned distal to the wye-piece in the ventilator circuit and use breath actuation to deliver the dose only during inhalation. Such a system was used in a Phase 2 trial of a 400-mg dose of amikacin sulfate. Two thirds of patients receiving doses twice daily had tracheal concentrations of greater than 6,400 μg/mL, which was approximately sixfold higher than the peak concentration reported with a continuously running jet nebulizer.[11,14] This system is now being tested in two Phase 3 trials.

The system described herein included a combination of amikacin and fosfomycin, which has been previously reported as synergistic against highly resistant Gram-negative bacteria.[10] The highest amikacin resistance seen in a worldwide 35,000 patient surveillance study was an MIC of 256 μg/mL when tested against the 5:2 (by weight) amikacin/fosfomycin formulation.[10] In addition, fosfomycin has bactericidal activity against methicillin-resistant *Staphylococcus aureus* at low MICs.[15] As measured by laser diffractometry (Mastersizer X, Malvern, UK), the average mass median diameter (MMD) of the amikacin/fosfomycin (5:2) solution increased from 2.9 to 3.3 μm after humidification (personal communication, PARI Pharma). The pH of the formulation was corrected with HCl, which was chosen to provide a permeable anion to the antibiotic mixture, the absence of which is known to induce cough.[16]

An in-line vibrating membrane nebulizer (Investigational eFlow® Inline Nebulizer System, PARI Pharma GmbH, Starnberg, Germany), placed on the inspiratory arm, with a small (initial ≈ 3 μm MMD) droplet size was used to deliver the amikacin/fosfomycin combination in the reported study. This approach was chosen to accomplish multiple goals. First, the small particle size was chosen to allow the ventilator humidity to remain on during drug delivery, while minimizing potential rainout in the tubing. The ability to leave the ventilator humidity on is important, because use of nonhumidified circuits is not standard of care, and increases in the incidence of tracheal tube occlusion are observed with the use of heat moisture exchangers.[17] Second, the same nebulizer stays in place for the entire treatment period, avoiding repeated opening of the ventilator circuit, which would increase the likelihood of contamination. Finally, the eFlow Inline System delivers potentially therapeutic concentrations rapidly. During continuous nebulization, using a low bias flow (less than 3 L/min) creates a ''reservoir'' function in the inspiratory arm between the nebulizer and wye-piece connector, thus providing a dense bolus of aerosolized drug at the onset of each inspiration.[18]

This article reports a Phase 1 pharmacokinetics and safety study of the amikacin plus fosfomycin combination delivered with the eFlow Inline System in patients receiving mechanical ventilation.

Materials and Methods

The Phase 1 study was a randomized, double-blind, placebo-controlled, dose-escalation study of amikacin and fosfomycin (50 mg/mL amikacin base and 20 mg/mL fosfomycin disodium salt, pH corrected to 5–7 with HCl) delivered via the eFlow Inline System in mechanically ventilated patients with either ventilator-associated pneumonia (VAP) or ventilator-associated tracheobronchitis (VAT). The study was conducted at the Intensive Care Unit (ICU) of the Alfred Hospital in Melbourne, Australia (a 45-bed, level 3, multidisciplinary ICU that treats approximately 2,000 patients per annum) and was approved by the hospital's Human Research Ethics Committee. The study was prospectively registered with the Australian New Zealand Clinical Trials registry (ACTRN 12612000273886).

Inclusion criteria were: male or female patients ≥18 years and ≤80 years of age with clinical diagnosis of VAP or VAT[19] and expected to be on mechanical ventilation for at least 3 days; Gram-positive or Gram-negative bacteria on Gram stain of the tracheal aspirate; informed consent obtained from a legally authorized representative; and ability to produce at least 1 mL of tracheal aspirate. Exclusion criteria were: severely compromised or suppressed immune system prior to hospital admission; fraction of inspired oxygen (FiO_2) > 0.8 at enrollment; relative hypoxemia (O_2 saturation < 93% on an $FiO_2 \leq 0.8$) at enrollment; positive end-expiratory pressure (PEEP) > 15 cm H_2O at enrollment; creatinine > 0.18 mmol/L; positive pregnancy test or breast feeding; burns to greater than 40% of the body; treatment with systemic amikacin or fosfomycin within 48 hr of dosing; history of previous allergy or sensitivity to amikacin or fosfomycin; participation in a clinical study with administration of an investigational drug product within 3 months of study drug administration; blood hemoglobin < 70 g/L at enrollment; and any other condition that in the view of the Investigator was likely to interfere with the study or put the patient at risk.

The eFlow Inline System (PARI Pharma GmbH) was positioned in the inspiratory tubing between the Puritan Bennett 840 Ventilator and the patient, 15 cm upstream of the wye-piece connector, and remained in place until the course of therapy was completed. The ventilator humidifier was left on during study drug administration, and the site was instructed to set bias flow at ≤2 L/min.

For each cohort, patients were to receive three ascending doses of study drug, with one dose administered every 22–26 hr. On day 3, patients were to receive one dose of study drug and one dose of volume-matched placebo (0.9% normal saline) administered 2 hr apart; day 3 treatments were blinded and randomized to order. The treatment order of amikacin/fosfomycin and placebo on day 3 was allocated by way of a randomization schedule prepared by a third-party statistician. A copy of the randomization code was kept on file at the investigational pharmacy. An unblinded pharmacist prepared study drug for dosing and labeled each dose in a blinded manner to ensure the investigator, ICU staff, and patient/family members remained blinded.

Cohorts were planned to be dosed as follows: cohort 1 ($n=3$): 2 mL (100 mg/40 mg amikacin/fosfomycin), 4 mL (200 mg/80 mg amikacin/fosfomycin), and 6 mL (300 mg/120 mg amikacin/fosfomycin); cohort 2 ($n=3$): 4 mL (200 mg/80 mg amikacin/fosfomycin), 6 mL (300 mg/120 mg amikacin/fosfomycin), and 8 mL (400 mg/160 mg amikacin/fosfomycin); cohort 3 ($n=3$): 6 mL (300 mg/120 mg amikacin/fosfomycin), 8 mL (400 mg/160 mg amikacin/fosfomycin), and 10 mL (500 mg/200 mg amikacin/fosfomycin); and cohort 4 ($n=6$): 8 mL (400 mg/160 mg amikacin/fosfomycin), 10 mL (500 mg/200 mg amikacin/fosfomycin), and 12 mL (600 mg/240 mg amikacin/fosfomycin). It was determined that there was no need to proceed with cohort 4 based on the findings of high concentrations of study drug in tracheal aspirate samples from patients in cohorts 1, 2, and 3; the higher doses slated for testing in cohort 4 would not be used in future studies with the amikacin/fosfomycin combination.

As this was not a powered efficacy study, no formal sample size calculations were performed. The number of patients proposed per cohort was considered sufficient for an exploratory study to assess the pharmacokinetics of escalating doses of nebulized amikacin/fosfomycin.

Amikacin and fosfomycin systemic concentrations were measured at pre-dose, 10 min, 1, 2, 4, 6, and 24 (± 2) hr post dose. Amikacin and fosfomycin tracheal aspirate concentrations were measured at pre-dose, 15 min, 1, 2, 4, 6, and 24 (± 2) hr post dose. Amikacin and fosfomycin concentrations were determined by the high-performance liquid chromatography–tandem mass spectrometry method. The following parameters were calculated for each dose: C_{max}, T_{max}, and area under the concentration–time curve from time 0 to 24 hr (AUC_{0-24}). Tracheal aspirate samples were collected by suctioning via the endotracheal tube into preweighed, tracheal aspirate traps. If a sample could not be obtained with suction alone, a small amount (1–3 mL) of sterile saline was flushed into the endotracheal tube and then suctioned back. Samples were frozen for shipment to a laboratory for analysis by liquid chromatography–tandem mass spectrometry.

Safety parameters evaluated included adverse events, laboratory parameters (serial hematology, biochemistry, and urinalysis), airway peak and plateau pressures before and after drug administration, and oximetry before and during drug administration.

Statistical methods

All pharmacokinetic parameters were summarized using descriptive statistics and presented by time point and dose. All safety parameters were summarized using descriptive statistics and presented by time point and dose.

Results

A total of nine patients were randomized, and eight (all male, age range 28–80 years) were dosed during the study (Table 1). One patient had a clinical deterioration between consent and planned study drug dosing and was withdrawn from the study. Of the eight patients dosed, seven had VAP and one had VAT. Five patients had exclusively Gram-negative bacteria, two had both Gram-negative and Gram-positive bacteria, and one patient had only Gram-positive bacteria. All were receiving appropriate concomitant systemic antibiotic therapy.

All treatments were well tolerated with no clinically meaningful changes in oximetry, airway pressures, vital signs, monitored cardiac telemetry, clinical chemistries, or hematology. Delivery time averaged 2 min per milliliter of solution. All patients were on a spontaneous triggered ventilation mode (set rate = 0) with mean ± SD delivered tidal volume of 551 ± 54 mL (range 382–750 mL). FiO_2 ranged from 0.3 to 0.5, and PEEP ranged from 5 to 12.5 cm H_2O. No clinically meaningful trends were observed in FiO_2 or PEEP in response to study drug administration. Three patients (one from each cohort) demonstrated an improved clinical condition during study participation, and were extubated or removed from mechanical ventilation prior to the planned third dose. The patient who was not administered study drug due to deteriorating clinical condition was assigned to cohort 3.

Amikacin plasma and tracheal aspirate pharmacokinetics

The amikacin plasma and tracheal aspirate pharmacokinetics are presented in Table 2. These data demonstrate that amikacin was rapidly absorbed following administration with the eFlow Inline System. The profiles also show rapid clearance of amikacin, with plasma levels returning to baseline within 24 hr following dosing in most patients, with the exception of one patient, who still had quantifiable plasma amikacin 24 hr after dosing on day 2. Mean C_{max} and AUC_{0-24} increased with dose.

The amikacin tracheal aspirate peak concentrations were achieved at the first measurement for all patients at all doses with rapid clearance. Amikacin C_{max} in tracheal aspirate increased with the 100/40 mg and 200/80 mg doses, and then plateaued at the 300/120 mg and 400/160 mg doses.

Fosfomycin plasma and tracheal aspirate pharmacokinetics

The fosfomycin plasma and tracheal aspirate pharmacokinetics are presented in Table 3. These data demonstrate that fosfomycin was rapidly absorbed following administration with the eFlow Inline System. The profiles also show rapid clearance of fosfomycin, with plasma levels returning to baseline within 24 hr following dosing in most patients, with the exception of one patient, who still had quantifiable fosfomycin in plasma at 24 hr after dosing on day 2. Both mean C_{max} and AUC_{0-24} increased with dose.

Tracheal aspirate C_{max} and AUC_{0-24} showed no relationship to dose. The mean C_{max} appeared to plateau at approximately 6,000 μg/g following administration of the 200/80 mg, 300/120 mg, and 400/160 mg doses. As observed for amikacin, mean T_{max} occurred at the first observation for all doses. For the 300/120 mg dose, C_{max} was observed at 15 min; 6 hr after dosing, the mean concentration was 225.5 μg/g, and at 24 hr it was below the lower limit of quantitation (10.0 μg/g).

Discussion

The purposes of this Phase 1 study were to determine the pharmacokinetics, safety, and tolerability of nebulized

Table 1. Patient Characteristics

	Treatment group			
	Cohort 1 (n = *3*)	*Cohort 2* (n = *3*)	*Cohort 3* (n = *2*)	*Overall* (n = *8*)
Age (years), mean (SD)	60.3 (20.0)	52.3 (24.5)	49.5 (27.6)	54.6 (20.5)
Age (years), range	40–80	28–77	30–69	28–80
Male, *n* (%)	3 (100)	3 (100)	2 (100)	8 (100)
Creatinine (μmol/L) at screening, mean (range)	66.3 (52, 80)	93.3 (61, 113)	72.5 (59, 86)	78.0 (52, 113)
Race, *n* (%)				
White	2 (66.7)	3 (100)	1 (50.0)	6 (75.0)
Arabic	0 (0)	0 (0)	1 (50.0)	1 (12.5)
Australian Aborigine/Torres Strait Islander	1 (33.3)	0 (0)	0 (0)	1 (12.5)
Reason for mechanical ventilation, *n* (%)				
Trauma[a]	2 (67.2)	3 (100)	1 (50.0)	6 (75.0)
Idiopathic cardiomyopathy	0 (0)	0 (0)	1 (50.0)	1 (12.5)
Myocardial infarction and cerebrovascular accident	1 (33.3)	0 (0)	0 (0)	1 (12.5)
Findings on baseline chest x-ray, *n* (%)				
Left lower lobe infiltrate	1 (33.3)	2 (67.7)	1 (50.0)	4 (50.0)
Right lower lobe infiltrate	1 (33.3)	1 (33.3)	0 (0)	2 (25.0)
Right middle lobe infiltrate	1 (33.3)	0 (0)	0 (0)	1 (12.5)
No infiltrate	0 (0)	0 (0)	1 (50.0)	1 (12.5)
Cause of infection, *n* (%)				
Gram-positive bacteria	0 (0)	1 (33.3)	0 (0)	1 (12.5)
Gram-negative bacteria	2 (66.6)	1 (33.3)	2 (100)	5 (62.5)
Gram-positive and Gram-negative bacteria	1 (33.3)	1 (33.3)	0 (0)	2 (25.0)
Indication for study, *n* (%)				
VAP	3 (100)	3 (100)	1 (50.0)	7 (87.5)
VAT	0 (0)	0 (0)	1 (50.0)	1 (12.5)

[a]Trauma: 1, subarachnoid hemorrhage and rib fractures; 2, head trauma and intracerebral hemorrhage; 3, liver laceration, rib fractures, and pulmonary contusions; 4, multiple spinal fractures; 5, multiple spinal fractures, multiple rib fractures, left hemopneumothorax, fractured pelvis, and closed head injury; and 6, road accident.

amikacin/fosfomycin in patients with a clinical diagnosis of VAP or VAT following delivery via PARI Pharma's Investigational eFlow Inline Nebulizer System and to evaluate doses of amikacin/fosfomycin for subsequent efficacy studies.

A total of eight adult male patients were enrolled and randomized, and then received at least two ascending doses of study drug. The majority of these critically ill patients had a clinical diagnosis of VAP. The systemic and tracheal aspirate pharmacokinetics of nebulized amikacin and fosfomycin were assessed. The shape of the plasma profiles for both amikacin and fosfomycin indicated rapid absorption, with rapid elimination post dose for both active ingredients. The peak concentrations for both amikacin and fosfomycin at all doses were well below the peak concentrations observed after typical systemic doses.[20–22] There was a trend toward a linear relationship between mean C_{max} and dose for amikacin and fosfomycin, and between AUC and dose for amikacin and fosfomycin. Tracheal aspirate C_{max} levels peaked at the 300/120 mg dose for amikacin and fosfomycin. There was no apparent relationship between AUC and dose for either amikacin or fosfomycin in tracheal aspirate. Mean peak amikacin in tracheal aspirate was approximately 12,000 μg/mL for the 300/120 mg and 400/160 mg doses. This concentration is more than 46-fold higher than the MIC of amikacin for the most resistant isolate observed in supportive *in vitro* studies, including evaluations of the susceptibility of highly resistant strains.[10] The bactericidal activity of amikacin is related to peak concentration. Therefore, even in the absence of a synergistic effect of fosfomycin,[10] the levels of amikacin achieved after administration of the 300/120 mg dose would be high enough to overcome any sputum inhibition and be effective against most sensitive strains; however, higher concentrations would be required for activity against highly amikacin-resistant strains, as a 25-fold multiple of the MIC is required for bactericidal activity.[11,12]

It is difficult to compare antibiotic concentrations achieved using different devices and in different patient populations. Nonetheless, we did not expect to observe a 10-fold increase in antibiotic concentrations when the amikacin tracheal aspirate concentrations in this study (administration with eFlow Inline System to patients on mechanical ventilation) were compared with tobramycin sputum concentrations reported in a previous study (administration with PARI LC PLUS jet nebulizer to cystic fibrosis patients).[1] The systemic antibiotic levels were low and comparable in both VAP and cystic fibrosis patients. The differences in tracheal concentrations may reflect application via mechanical ventilation versus spontaneous breathing, but also raise the possibility that the lower sputum volume in a patient with VAP compared with a patient with cystic fibrosis may lead to substantially higher tracheal antibiotic concentrations.

Fosfomycin bactericidal activity is dependent on the time above the MIC; therefore, based on these results and historical MIC data, twice daily (BID) therapy with the 300/120 mg dose will provide 24-hr coverage for inhibition of

Table 2. Amikacin Pharmacokinetic Parameters

	Amikacin/fosfomycin dose				
	100/40 mg (n = 3)	*200/80 mg (n = 6)*	*300/120 mg (n = 7)*	*400/160 mg (n = 4)*	*500/200 mg (n = 1)*
			Plasma		
T_{max} (hr)					
Mean (SD)	1.144 (0.901)	2.156 (1.149)	1.631 (0.877)	3.150 (0.947)	1.15
Median (range)	1.100 (0.27–2.1)	2.158 (1.03–4.2)	1.200 (1.02–3.3)	2.975 (2.25–4.4)	
C_{max} (ng/mL)					
Mean (SD)	166.00 (58.20)	374.00 (200.21)	612.43 (362.40)	837.00 (355.91)	1,370.0
Median (range)	137.00 (128.0–233.0)	319.00 (168.0–667.0)	471.00 (360.0–1,380.0)	760.50 (497.0–1,330.0)	
AUC_{0-24} (hr*μg/g)					
Mean (SD)	555.08 (212.79)	2,893.51 (1,475.52)	5,829.81 (1,983.49)	7,394.82 (2,466.32)	4,402.4
Median (range)	502.43 (373.6–789.3)	3,339.77 (651.7–4,240.8)	5,192.22 (3,622.5–8,969.4)	7,201.57 (5,006.4–10,169.7)	—
			Tracheal aspirate		
T_{max} (hr)					
Mean (SD)	0.361 (0.054)	0.714 (0.769)	0.448 (0.038)	1.542 (1.263)	0.35
Median (range)	0.383 (0.3–0.4)	0.40 (0.38–2.28)	0.450 (0.38–0.50)	1.517 (0.42–2.72)	—
C_{max} (μg/g)					
Mean (SD)	6,103.33 (1,422.90)	9,303.33 (5,616.67)	12,390.00 (3,986.97)	11,617.50 (1,954.11)	14,200.0
Median (range)	5,410.00 (5,160.0–7,740.0)	9,365.00 (2,850.0–15,700.0)	11,400.00 (6,910.0–17,000.0)	11,400.00 (9,470.0–14,200.0)	—
AUC_{0-24} (hr*μg/g)					
Mean (SD)	10,181.44 (4,279.67)	28,549.68 (36,433.09)	19,280.42 (13,307.43)	18,420.94 (6,634.08)	13,800.6
Median (range)	10,561.68 (5,724.3–14,258.3)	16,189.64 (7,491.2–101,931.3)	14,084.25 (8,480.9–41,763.8)	18,679.11 (10,762.2–25,563.3)	—

Table 3. Fosfomycin Pharmacokinetic Parameters

	Amikacin/fosfomycin dose				
	100/40 mg (n = 3)	*200/80 mg (n = 6)*	*300/120 mg (n = 7)*	*400/160 mg (n = 4)*	*500/200 mg (n = 1)*
Plasma					
T_{max} (hr)					
Mean (SD)	2.033 (1.733)	1.858 (1.363)	1.340 (0.473)	1.958 (1.248)	1.15
Median (range)	1.1 (0.97–4.03)	1.6 (0.30–4.22)	1.2 (1.02–2.40)	2.0 (0.57–3.33)	—
C_{max} (ng/mL)					
Mean (SD)	128.47 (70.19)	247.58 (172.30)	391.00 (202.02)	492.75 (217.46)	541.0
Median (range)	137.00 (54.4–194.0)	239.00 (67.0–446.0)	327.00 (195.0–738.0)	426.9 (324.0–795.0)	—
AUC_{0-24} (hr*μg/g)					
Mean (SD)	879.49 (548.01)	1,828.49 (1,203.67)	2,994.01 (840.41)	3,389.02 (789.96)	1,822.0
Median (range)	1,080.92 (259.3–1,298.28)	1,643.79 (575.9–3,678.13)	2,753.40 (2,191.5–4,506.35)	3,168.06 (2,699.7–4,520.31)	—
Tracheal aspirate					
T_{max} (hr)					
Mean (SD)	0.36 (0.054)	0.40 (0.013)	0.45 (0.038)	1.54 (1.263)	0.35
Median (range)	0.383 (0.300–0.400)	0.400 (0.383–0.417)	0.450 (0.383–0.500)	1.517 (0.417–2.717)	—
C_{max} (μg/g)					
Mean (SD)	3,863.33 (75.06)	6,055.00 (4,454.19)	6,174.29 (2,548.07)	6,072.50 (1,935.16)	5,680.0
Median (range)	3,860.00 (3,790.00–3,940.00)	5,275.00 (1,740.00–13,800.00)	6,650.00 (2,930.00–10,000.00)	5,940.00 (3,850.00–8,560.00)	—
AUC_{0-24} (hr*μg/g)					
Mean (SD)	6,830.67 (1,603.46)	13,206.33 (11,737.84)	10,409.67 (7,393.95)	10,740.10 (7,563.37)	6,304.2
Median (range)	7,570.54 (4,990.87–7,930.61)	9,650.32 (4,121.11–34,685.70)	7,072.46 (4,335.98–21,478.45)	8,838.55 (4,127.20–21,156.11)	—

typical Gram-negative and Gram-positive pathogens associated with pneumonia in mechanically ventilated patients.[15,23] However, for highly fosfomycin-resistant strains, levels would not exceed the MIC for more than 6–8 hr over a 24-hr period, even with BID dosing.

The peak amikacin tracheal concentrations achieved with the 300/120 mg dose of amikacin/fosfomycin were higher than what was reported with a 400-mg dose of amikacin sulfate using the breath-actuated vibrating plate nebulizing system.[11] This suggests that the approach of using the inspiratory limb as a reservoir could result in comparable or superior *in vivo* results compared with breath-actuated nebulization. The approach used in this study also resulted in a faster delivery time than was reported for the breath-activated system, and allowed the same nebulizer to remain in the inspiratory limb for the duration of therapy.

The evaluation of safety and tolerability of amikacin and fosfomycin was another study objective. There were no dose-related effects on laboratory values, vital signs, oximetry, airway pressure, or ventilator settings. Adverse events of interest included oxygen desaturation, increased peak airway pressure, bronchospasm, increased creatinine, and cardiac arrhythmias. None of these were observed during the study at any dose level.

Based on review of the safety data, all assessed doses of amikacin/fosfomycin were deemed to be safe and well tolerated in this patient population. We have initiated a Phase 2 multicenter international study of the 300/120 mg amikacin/fosfomycin dose as adjunctive therapy to intravenous antibiotics for Gram-negative bacterial pneumonia in patients on mechanical ventilation.[24]

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Author Disclosure Statement

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