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Pharmacokinetics (PK) and Safety of Single Doses of Delafloxacin Administered Intravenously in Healthy Human Subjects

Laura Lawrence[1], Michael Benedict[2], James Hart[2], Allan Hawkins[2], Danping Li[1], Matthew Medlock[2], Scott Hopkins[1], and Eric Burak[3]

[1]Rib-X Pharmaceuticals, New Haven, CT, [2]PPD Phase I Clinic, Austin, TX, [3]Theracos, New York, NY

New Haven, CT 06511 Phone: 203-624-5606 www.Rib-X.com

Abstract

Background
Delafloxacin (DFX) is an investigational fluoroquinolone (FQ) with potent activity against a variety of Gram-positive and Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus*. The optimal dosing of FQs in a clinical setting is dependent on exposure in human subjects and an adequate safety profile.

Methods
The safety, tolerability and PK of delafloxacin at 300, 450, 600, 750, 900, and 1200 mg single intravenous doses was explored in a randomized, double blind, placebo controlled study.
All doses were administered as 1-hour infusions to fasted subjects. Safety assessments were evaluated by collection of adverse events (AEs) and clinical laboratory evaluations including hematology, serum chemistry, and urinalysis, vital sign measurements, 12-lead electrocardiogram results, and physical examination. Dose proportionality analyses using a power model were performed on $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}last}$ and C_{max}. Plasma and urine PK parameters of delafloxacin were summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, maximum, and coefficient of variation) for each dose group for up to 48 hours.

Results
Ten subjects per dose group received DFX or placebo. After single doses of DFX, mean C_{max} ranged from 10.4 – 49.1 µg/ml and $AUC_{0\text{-}\infty}$ ranged from 24.8 – 160.0 µg/mL*h over the dose range with increases proportionate to dose. Clearance was roughly consistent from 300 to 900 mg (12.5 – 9.7 L/h) with 1200 mg demonstrating a notable reduction. All AEs were mild to moderate, were generally gastrointestinal in nature, and resolved within 24 hours. The percentages of subjects that experienced gastrointestinal disorders for each dose were 8.3% (300 mg), 0% (450/600 mg), 25% (750 mg), 37.5% (900 mg), 87.5% (1200 mg), and 10% (placebo). At the dose group of 1200 mg, 75% of subjects experienced emesis and 50% nausea, and therefore 900 mg is expected to be the maximum tolerated intravenous dose.

Conclusions
Delafloxacin was found to be safe and well tolerated in normal healthy subjects at doses up to 900 mg. $AUC_{0\text{-}\infty}$ and C_{max} parameters increased proportionately with dose. The data supports further development of delafloxacin in Phase 2 and 3 clinical studies.

Introduction

Delafloxacin (RX-3341) is an investigational antibiotic of the fluoroquinolone class distinguished by its excellent antibacterial activity against gram-positive organisms including both methicillin-susceptible *Staphylococcus aureus* and MRSA. Delafloxacin provides antimicrobial coverage of prevalent MRSA and methicillin resistant coagulase negative staphylococci. In general, the *in vitro* antibacterial activity of delafloxacin is more potent than that of levofloxacin and ciprofloxacin against most quinolone susceptible pathogens, including species responsible for surgical site infections, community and nosocomial respiratory tract infections, urinary tract infections, blood stream infections, skin and skin structure infections, and anaerobic infections. Delafloxacin is more active than levofloxacin against most gram-positive pathogens and notably is 64 fold more active than levofloxacin against MRSA isolates including 71% of levofloxacin nonsusceptible isolates. Delafloxacin has good activity (minimum inhibitory concentration required to inhibit the growth of 90% of isolates [MIC_{90}] values of ≤0.25 µg/mL) against gram negative organisms that are susceptible to levofloxacin.

Methods

This was a double-blind, randomized, placebo-controlled, single IV maximum tolerated dose study with delafloxacin or placebo. All doses of delafloxacin were administered as a 1 hour infusion. Subjects were assigned sequentially. On Day 1, 10 subjects per group received a single IV infusion of 450-, 600-, 750-, 900-, or 1200-mg delafloxacin or placebo (8:2), according to the randomization schedule. The 450 mg and 600 mg dose levels were administered to assigned subjects concurrently.

Subjects fasted overnight for at least 8 hours before dosing and continued to fast for 4 hours after dosing. Standard meals were provided while subjects were confined to the clinical unit. Blood for plasma samples were collected before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20, 24, 30, 36, and 48 hours after initiation of dosing. Urine samples were collected from –2 to 0 hours before dosing and at the following intervals after initiation of dosing: 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours, and 24 to 48 hours.

Adverse events (AEs) were monitored from Check in through the follow-up visit in both parts of the study. Serum and urine samples for clinical laboratory assessments (Table 1) and vital sign measurements were obtained at Screening, Check-in, before dosing (Day 1), before Check out (Day 4), and at Follow-up (Day 9 [±2 days]). Twelve lead electrocardiograms (ECGs) were performed at Screening, Check-in, before dosing on Day 1, after completion of the IV infusion, before Check-out, and at Follow-up. A complete physical examination was performed at Screening, before Check-out, and at Follow up. A brief physical examination was performed at Check in and 4 hours after initiation of dosing.

Subjects for both parts were screened approximately 4 weeks (Days –28 to –1) before the first dose of study drug and checked into the clinical unit on Day –1. Subjects resided at the clinical unit for a total of 4 nights. Each subject returned for a follow up visit on Day 9 (± 2 days) (Figure 2). A schedule of events is given in Table 2.

For the purpose of calculating PK parameters, all concentrations that were below the limit of quantification (BLQ) before the first measurable concentration were set to 0, and a concentration that was BLQ was set to missing if it was between 2 measurable concentrations. Any BLQ values that occurred at the end of the plasma concentration versus time profile were set to 0. PK parameters were determined from plasma and urine concentrations of delafloxacin by noncompartmental methods using SAS® software Version 9.1 or higher (SAS Institute Inc, Cary, North Carolina): See Table Definition of PK Parameters

Plasma was obtained from blood samples collected for PK analysis at the time points indicated in Table 2. Blood (10 mL) was collected into chilled (2°C to 8°C) tubes containing dipotassium EDTA, mixed by gently inverting 2 to 3 times and stored in cryoblocks until they were centrifuged. Within 20 minutes of collection, samples were centrifuged under refrigeration (2°C to 8°C) at 900g for 15 minutes, split into 2 aliquots and transferred into chilled polypropylene tubes. The samples were stored frozen at 70°C or colder until shipment.

Urine was obtained from at the time points indicated in Table 2. Subjects were instructed to empty their bladder completely at the start and end of each interval. After collection, each urine sample was stored in a chilled container, and the urine volume and time of collection were recorded. At the end of each interval, all voids collected were pooled, thoroughly mixed, and the total urine volume was measured. For PK analysis, duplicate aliquots (10 mL) were transferred to chilled containers and then frozen at –70°C until shipment.

Adverse Events were coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 13.1) by system organ class (SOC) and preferred term. Clinical laboratory test results (hematology [including coagulation assays], serum chemistry, and urinalysis), vital sign measurements (oral temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate), and quantitative 12 lead ECG results were summarized by actual results and change from Baseline. Physical examination findings were listed.

Table 1 - Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Absolute neutrophil count with autodifferential	Alanine aminotransferase	Bilirubin
Hematocrit	Albumin	Blood
Hemoglobin	Alkaline phosphatase	Color
Leukocytes (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)*	Anion gap	Glucose
Mean corpuscular hemoglobin	Aspartate aminotransferase	Ketones
Mean corpuscular hemoglobin concentration	Blood urea nitrogen	Leukocyte esterase
Mean corpuscular volume	Calcium	Nitrite
Platelet count	Carbon dioxide	pH
Red blood cell count	Chloride	Protein
Red cell distribution width	Creatinine	Specific gravity
	Glucose	Turbidity
Coagulation parameters	Gamma-glutamyltransferase	Urobilinogen
International normalized ratio	Lactate dehydrogenase	
Partial thromboplastin time	Phosphorous	
Prothrombin time	Potassium	
	Sodium	
	Total bilirubin	
	Total cholesterol	
	Total protein	
	Triglycerides	
	Uric acid	

*Reported as both absolute counts and percentage of the total white blood cell count.

Table 2 - Schedule of Events

	Screening	Check-in	Treatment Period	Check-out	Follow-up
Event/Study Day	Days –28 to –1	Day –1	Day 1	Day 4	Day 9 (± 2 days)
Informed consent	X				
Inclusion /exclusion criteria	X				
Medical history	X	X			
Demographic information	X				
Electrocardiogram (12-lead)	X	X	X	X	X
Urine drug and alcohol screen	X	X			
Serology	X				
Pregnancy test	X	X			
Physical examination	X	X	X	X	X
Vital sign measurements	X	X	X	X	X
Clinical laboratory tests	X	X	X	X	X
Drug administration			X		
Pharmacokinetic sample collection			X		
Prior and concomitant medications	X	X	X	X	X
Adverse event monitoring		X	X	X	X

Results

All 62 subjects (100.0%) completed the study and no subjects were discontinued (Table 3). Demographic characteristics were similar across treatment groups (Table 4).

Pharmacokinetics

Following single IV dose administration of 300, 450, 600, 750, 900, and 1200 mg delafloxacin, total exposure (AUC) increased more than dose proportionally but C_{max} appeared to increase dose proportionally (Figure 3; Table 5 – 7). The mean $t_{1/2}$ values of delafloxacin ranged from 8.21 to 17.74 hours, with mean values near 12 hours for most dose levels. Mean CL values decreased from 12.53 L/h at the 300 mg dose to 7.59 L/h at the 1200 mg dose.

Mean fractions of the drug excreted unchanged in urine within 12 hours after a single dose of delafloxacin ranged from 30% to 38% with an approximate additional 2% excreted over the following 36 hours. Mean renal clearance of delafloxacin tended to decrease with increasing dose of delafloxacin.

Safety

Overall, 41 TEAEs were reported and 18 of 62 subjects (29.0%) experienced at least 1 TEAE (Table 8). The most frequently reported TEAEs overall were classified as gastrointestinal disorders (23.0%) and nervous system disorders (10.0%). The highest percentage of subjects (100.0%) reported TEAEs after receiving delafloxacin 1200 mg. Similar percentages of subjects reported TEAEs for delafloxacin 300 mg (16.7%), 750 mg (37.5%), 900 mg (37.5%), and placebo (20.0%). No TEAEs were reported by subjects after receiving delafloxacin 450 mg or 600 mg. The majority of TEAEs were of mild severity and were possibly or probably related to study drug. Ten moderate TEAEs were reported after delafloxacin 1200 mg. All TEAEs considered probably related to study drug were reported after delafloxacin 1200 mg.

There were no deaths, SAEs, or AEs leading to study discontinuation, and all TEAEs resolved by the end of the study. There were no clinically significant abnormal laboratory results and none of the individual hematology, serum chemistry, or urinalysis results outside the reference range were considered clinically significant by the principal investigator or reported as TEAEs.

Table 3 - Summary of Subject Disposition (All Subjects)

	Placebo (n=10)	Delafloxacin 300 mg (n=12)	Delafloxacin 450 mg (n=8)	Delafloxacin 600 mg (n=8)	Delafloxacin 750 mg (n=8)	Delafloxacin 900 mg (n=8)	Delafloxacin 1200 mg (n=8)	Overall (n=62)
Total number of subjects, n (%)								
Completed	10 (100.0%)	6 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	62 (100.0%)
Discontinued	0	0	0	0	0	0	0	0
Safety population	10 (100.0%)	6 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	62 (100.0%)
Pharmacokinetic population	0	6 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	52 (84.0%)

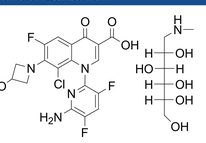
Note: Percentages were based on the number of subjects enrolled in each treatment for the completed, discontinued, and safety population rows, and were based on the number of subjects in the safety population for all other rows.

Table 5 - Mean (CV) Plasma Pharmacokinetic Parameters of Delafloxacin (Pharmacokinetic Population)

Treatment Parameter (unit)	Delafloxacin 300 mg (n=12)	Delafloxacin 450 mg (n=8)	Delafloxacin 600 mg (n=8)	Delafloxacin 750 mg (n=8)	Delafloxacin 900 mg (n=8)	Delafloxacin 1200 mg (n=8)
$AUC_{0\text{-}t}$ (µg*h/mL)[a]	23.63 (19)	40.56 (17)	58.59 (26)	70.61 (25)	92.42 (28)	146.93 (18)
$AUC_{0\text{-}\infty}$ (µg*h/mL)	24.74 (0)	42.61 (17)	61.48 (24)	74.04 (27)	98.13 (29)	155.56 (18)
$AUC_{0\text{-}last}$ (µg*h/mL)	24.83 (20)[b]	42.87 (17)	59.03 (23)[d]	74.43 (5)[e]	99.34 (26)[f]	160.02 (12)[f]
C_{max} (µg/mL)	10.43 (19)	16.08 (13)	23.00 (21)	26.15 (15)	29.66 (16)	49.06 (25)
T_{max} (h)[c]	1.00 (0.97, 1.08)	1.00 (1.00, 1.00)	1.02 (1.00, 1.03)	1.00 (1.00, 1.15)	1.00 (1.00, 1.03)	1.02 (0.80, 1.05)
CL (L/h)	12.53 (21)[b]	10.78 (18)	10.63 (22)[d]	10.09 (5)[e]	9.65 (29)[f]	7.59 (13)[f]
V_{SS} (L)	34.18 (20)[b]	36.63 (26)	38.46 (33)[d]	32.89 (13)[e]	36.40 (18)[f]	30.21 (14)[f]
V_Z (L)	146.13 (34)[b]	197.87 (56)	193.63 (66)[d]	257.21 (9)[e]	147.61 (51)[f]	131.37 (44)[f]
$t_{1/2}$ (h)	8.21 (33)[b]	12.45 (44)	11.92 (45)[d]	17.74 (14)[e]	11.64 (67)[f]	11.71 (34)[f]

Abbreviation: CV, coefficient of variation.
a tau = 12 hours
b n = 9
c Median (Minimum, Maximum)
d n = 7
e n = 3
f n = 6

Figure 1- Structure of Delafloxacin



Definition of PK Parameters

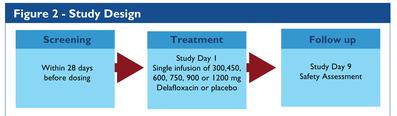
Plasma	
$AUC_{0\text{-}t}$	area under the concentration versus time curve from time 0 to 12 hours post dose, calculated using the linear trapezoidal rule
$AUC_{0\text{-}t}$	area under the plasma concentration versus time curve from time 0 (initiation of dosing) to the time of the last quantifiable concentration
$AUC_{0\text{-}\infty}$	area under the plasma concentration versus time curve from time 0 (initiation of dosing) extrapolated to infinity
%F	bioavailability, calculated by dividing $AUC_{0\text{-}\infty}$ following oral administration by $AUC_{0\text{-}\infty}$ following IV administration × 100 (Part 1 only)
CL	total body clearance
CL/F	apparent clearance total
C_{max}	maximum observed plasma concentration over entire concentration profile
T_{max}	time to achieve maximum observed plasma concentration
Kel	apparent terminal elimination rate constant obtained from the concentration data
$t_{1/2}$	apparent terminal elimination half life
Vd/F	apparent volume of distribution (oral treatment)
V_{SS}	volume of distribution at steady state
V_Z	volume of distribution (IV treatments)
Urine	
$Ae_{0\text{-}4}$	total amount excreted unchanged in urine from 0 to 4 hours after dosing
$Ae_{4\text{-}8}$	total amount excreted unchanged in urine from 4 to 8 hours after dosing
$Ae_{8\text{-}12}$	total amount excreted unchanged in urine from 8 to 12 hours after dosing
$Ae_{12\text{-}24}$	total amount excreted unchanged in urine from 12 to 24 hours after dosing
$Ae_{24\text{-}48}$	total amount excreted unchanged in urine from 24 to 48 hours after dosing
$Ae_{0\text{-}48}$	total amount excreted unchanged in urine from 0 to 48 hours after dosing
$Fe\%_{0\text{-}12}$	fraction of the dose excreted unchanged from 0 to 12 hours after dosing, calculated as $(Ae_{0\text{-}12}/Dose)*100$
$Fe\%_{0\text{-}24}$	fraction of the dose excreted unchanged from 0 to 24 hours after dosing, calculated as $(Ae_{0\text{-}24}/Dose)*100$
$Fe\%_{0\text{-}48}$	fraction of the dose excreted unchanged from 0 to 48 hours after dosing, calculated as $(Ae_{0\text{-}48}/Dose)*100$
CLr	renal clearance calculated as $Ae_{0\text{-}48}/AUC_{0\text{-}t}$

Table 4 - Demographic and Baseline Characteristics (Safety Population)

	Treatment						
	Placebo (N=10)	Delafloxacin 300 mg (N=12)	Delafloxacin 450 mg (N=8)	Delafloxacin 600 mg (N=8)	Delafloxacin 750 mg (N=8)	Delafloxacin 900 mg (N=8)	Delafloxacin 1200 mg (N=8)
Age (years)							
n	10	12	8	8	8	8	8
Mean	31.2	37.9	38.5	38.9	39.4	32.9	38.3
SD	9.65	13.43	14.62	10.33	12.02	13.6	14.92
Median	28	30.5	39	41	42	27.5	33.5
Minimum	21	22	21	25	22	19	24
Maximum	52	58	59	55	53	52	64
Sex, n(%)							
Male	6 (60.0%)	6 (50.0%)	5 (62.5%)	5 (62.5%)	4 (50.0%)	5 (62.5%)	4 (50.0%)
Female	4 (40.0%)	6 (50.0%)	3 (37.5%)	3 (37.5%)	4 (50.0%)	3 (37.5%)	4 (50.0%)
Race, n(%)							
White	9 (90.0%)	9 (75.0%)	6 (75.0%)	7 (87.5%)	7 (87.5%)	6 (75.0%)	5 (62.5%)
Black or African American	1 (10.0%)	3 (25.0%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	2 (25.0%)	3 (37.5%)
Asian	0	0	1 (12.5%)	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0
Ethnicity, n(%)							
Hispanic or Latino	4 (40.0%)	2 (16.7%)	4 (50.0%)	3 (37.5%)	1 (12.5%)	3 (37.5%)	4 (50.0%)
Not Hispanic or Latino	6 (60.0%)	10 (83.3%)	4 (50.0%)	5 (62.5%)	7 (87.5%)	5 (62.5%)	4 (50.0%)
Height (cm)							
n	10	12	8	8	8	8	8
Mean	170.74	167.29	169.53	170.39	165.6	172.9	165.15
SD	7.169	9	7.577	10.586	8.818	6.73	9.031
Median	173.55	169.9	168.65	174.3	165	172.75	164.4
Minimum	156.8	153.3	159.7	152.9	154	164.4	153.2
Maximum	179	178.5	181.9	180.8	183	182.2	178.5
Weight (kg)							
n	10	12	8	8	8	8	8
Mean	78.79	72.81	70.06	73.71	73.86	79.33	72.19
SD	14.417	13.178	8.8	8.539	10.73	10.487	14.911
Median	74.1	71.5	72.5	69.85	72.9	77.2	72.7
Minimum	60.1	56.3	56.5	66.4	60.4	67.9	50.8
Maximum	100.6	96.4	83.1	90.7	95.1	98.6	99.2
BMI (kg/m^2)							
n	10	12	8	8	8	8	8
Mean	26.87	25.81	24.34	25.44	26.94	26.54	26.29
SD	3.383	2.948	2.033	2.326	3.183	3.102	3.751
Median	26.45	24.45	24.95	26	26.95	27	26.8
Minimum	20.4	21.9	21.5	21.7	20.9	21.8	19.9
Maximum	31.4	30.3	26.6	28.4	31.1	30.2	31.1

Note: Percentages were based on the number of subjects in the safety population within each treatment and overall.

Figure 2 - Study Design



Results

Table 8 - Treatment-Emergent Adverse Events (Safety Population)

System Organ Class Preferred Term	Number (%) of Subjects by Treatment Group						
	Placebo (n=10)	Delafloxacin 300 mg IV (n=12)	Delafloxacin 450 mg IV (n=8)	Delafloxacin 600 mg IV (n=8)	Delafloxacin 750 mg IV (n=8)	Delafloxacin 900 mg IV (n=8)	Delafloxacin 1200 mg IV (n=8)	Overall (N=62)
Total number of adverse events	4	3	0	0	5	11	18	41
Subjects with at least 1 TEAE	2 (20.0)	2 (16.7)	0	0	3 (37.5)	3 (37.5)	8 (100.0)	18 (29.0)
Subjects with at least 1 treatment-related AE								
Possibly related	1 (10.0)	1 (8.3)	0	0	2 (25.0)	3 (37.5)	1 (12.5)	8 (13.0)
Probably related	0	0	0	0	0	0	7 (87.5)	7 (11.3)
Very likely/certainly related	0	0	0	0	0	0	0	0
Gastrointestinal disorders	1 (10.0)	1 (8.3)	0	0	3 (25.0)	3 (37.5)	7 (87.5)	14 (23.0)
Abdominal distension	0	1 (8.3)	0	0	0	0	0	1 (2.0)
Nausea	1 (10.0)	0	0	0	2 (25.0)	3 (37.5)	4 (50.0)	10 (16.0)
Vomiting	0	0	0	0	0	0	6 (75.0)	6 (10.0)
Diarrhoea	0	0	0	0	1 (12.5)	1 (12.5)	2 (25.0)	4 (6.5)
Abdominal pain	0	0	0	0	1 (12.5)	0	0	1 (2.0)
Retching	0	0	0	0	0	0	1 (12.5)	1 (2.0)
General disorders and administration site conditions	1 (10.0)	0	0	0	0	1 (12.5)	1 (12.5)	3 (5.0)
Feeling hot	0	0	0	0	0	1 (12.5)	1 (12.5)	2 (3.0)
Asthenia	0	0	0	0	0	1 (12.5)	0	1 (2.0)
Thirst	0	0	0	0	0	1 (12.5)	0	1 (2.0)
Vessel puncture site swelling	1 (10.0)	0	0	0	0	0	0	1 (2.0)
Nervous system disorders	1 (10.0)	1 (8.3)	0	0	1 (12.5)	2 (25.0)	1 (12.5)	6 (10.0)
Headache	1 (10.0)	0	0	0	0	2 (25.0)	0	3 (5.0)
Dizziness	0	1 (8.3)	0	0	0	1 (12.5)	1 (12.5)	3 (5.0)
Presyncope	0	0	0	0	1 (12.5)	0	0	1 (2.0)
Somnolence	1 (10.0)	0	0	0	0	0	0	1 (2.0)
Respiratory, thoracic and mediastinal disorders	0	1 (8.3)	0	0	0	0	1 (12.5)	2 (3.0)
Nasal congestion	0	1 (8.3)	0	0	0	0	1 (12.5)	2 (3.0)
Rhinorrhoea	0	0	0	0	0	0	1 (12.5)	1 (2.0)
Skin and subcutaneous tissue disorders	0	0	0	0	0	1 (12.5)	1 (12.5)	2 (3.0)
Hyperhidrosis	0	0	0	0	0	1 (12.5)	0	1 (2.0)
Pruritis	0	0	0	0	0	0	1 (12.5)	1 (2.0)

Abbreviation: IV, intravenous; TEAE, treatment-emergent adverse event.

Note: The total number of adverse events counts all TEAEs in the safety population. Subjects may have had more than 1 TEAE per system organ class and preferred term. At each level of subject summarization, a subject was counted once if he or she reported 1 or more events. The TEAEs were summarized by treatment at onset of the event. Adverse events were coded using MedDRA Version 13.1. Percentages were based on the number of subjects in the safety population who received the specified treatment.

Table 6 - Analysis of Dose Proportionality

Parameter (unit)	Estimated Slope for Ln (Dose)	90% Confidence Interval for the Slope	P-value (slope=1)
$AUC_{0\text{-}t}$ (µg*h/mL)	1.2790	(1.1700, 1.3880)	<0.0001
$AUC_{0\text{-}\infty}$ (µg*h/mL)	1.3064	(1.1969, 1.4158)	<0.0001
C_{max} (µg/mL)	1.0520	(0.9615, 1.1426)	0.3402

Note: The power model, ln(parameter) = a + b*ln(dose) + error, was used to estimate the slope, corresponding 90% confidence interval, and the P value testing dose proportionality (b=1).

Figure 3 - Mean (±SD) Plasma Concentrations of Delafloxacin Over Time by Treatment

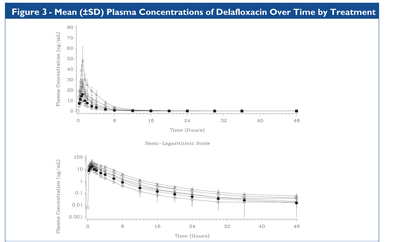


Table 7 - Mean (CV) Urinary Pharmacokinetic Parameters of Delafloxacin (Pharmacokinetic Population)

Treatment Parameter (unit)	Delafloxacin 300 mg (n=12)	Delafloxacin 450 mg (n=8)	Delafloxacin 600 mg (n=8)	Delafloxacin 750 mg (n=8)	Delafloxacin 900 mg (n=8)	Delafloxacin 1200 mg (n=8)
$Ae_{0\text{-}4}$ (mg)	94.56 (23)	124.38 (26)	175.73 (16)	175.60 (29)	211.54 (33)	246.74 (25)
$Ae_{4\text{-}8}$ (mg)	13.39 (64)	27.30 (15)	27.78 (47)	35.56 (51)	43.63 (68)	92.81 (44)
$Ae_{8\text{-}12}$ (mg)	4.79 (37)	5.87 (53)	12.62(33)	11.64 (76)	24.88 (47)	39.92 (41)
$Ae_{12\text{-}24}$ (mg)	2.28 (45)	4.57 (28)	6.72 (43)	7.25 (58)	16.16 (61)	18.01 (22)
$Ae_{24\text{-}48}$ (mg)	1.72 (89)	2.79 (43)	3.47 (44)	5.20 (44)	8.25 (50)	12.15 (48)
$Ae_{0\text{-}48}$ (mg)	116.74 (23)	164.91 (21)	226.31 (13)	235.26 (28)	304.46 (22)	409.65 (25)
$Fe\%_{0\text{-}12}$ (%)	37.58 (23)	35.01 (22)	36.02 (14)	29.71 (29)	31.12 (26)	31.62 (26)
$Fe\%_{0\text{-}24}$ (%)	38.34 (23)	36.03 (22)	37.14 (13)	30.67 (28)	32.91 (23)	33.12 (25)
$Fe\%_{0\text{-}48}$ (%)	38.91 (23)	36.65 (21)	37.72 (13)	31.37 (28)	33.83 (22)	34.14 (25)
CL, (L/h)	4.98 (33)	4.04 (34)	3.94 (25)	3.24 (25)	3.47 (51)	2.64 (19)

Abbreviation: CV, coefficient of variation.

Conclusions

- Delafloxacin C_{max} total exposure (AUC) increased greater than proportionally over the 300 to 1200 mg dose range.
- More than 30% of the drug was excreted unchanged in urine following single dose administration, with most of the drug excretion occurring within the first 12 hours after dosing.
- Mean renal clearance was approximately 5 L/h after administration of delafloxacin 300 mg and decreased to approximately 2.6 L/h as dose increased to 1200 mg.
- Overall 18 subjects (29%) reported a total of 41 TEAEs; the majority of these were mild and considered possibly related to delafloxacin. Overall, the largest number of subjects experienced TEAEs in the gastrointestinal disorders SOC (primarily nausea, vomiting, and diarrhea).
- Subjects in the 1200-mg treatment group reported the largest number of TEAEs, with most of these TEAEs of moderate severity and probably related to delafloxacin.
- Single IV infusions of delafloxacin at doses of 300, 450, 600, 750, and 900 mg were safe and well tolerated. A single IV infusion of 1200 mg delafloxacin was not as well tolerated.
- The maximum tolerated dose for a single IV infusion of delafloxacin was 900 mg.
- There were no clinically significant findings noted or TEAEs reported resulting from clinical laboratory assessments, vital sign measurements, ECG results, or physical examination findings.

References

[1]Rib X Pharmaceuticals, Inc. Delafloxacin (RX-3341). Investigator's brochure. Version 13.0. New Haven (CT); Dec 2010.