Poster A-1290
52nd ICAAC
San Francisco, CA
September 9-12, 2012

A Phase 1, Single and Multiple Ascending Intravenous (IV) Dose Study of Safety, and Pharmacokinetics (PK) of Radezolid (RDZ) in Healthy Subjects

L. LAWRENCE[1], A. MARRA[1], J. LONGCOR[1], R. HOOVER[1], E. BURAK[1], M. BENEDICT[2], C. SMITH[2], Y. CAI[2], M. MEDLOCK[2]

[1]Rib-X Pharmaceuticals, Inc., New Haven, CT; [2]PPD, Wilmington, NC

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

Abstract

Background
RDZ, an investigational oxazolidinone, has activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA).

Methods
A randomized, double-blind, placebo-controlled, single-center study evaluated the safety and PK of IV RDZ administered once daily for up to 14 days. A total of 64 male and female subjects 18 to 65 years old were randomly assigned to 1 of 8 groups. Each subject was administered a 1 hour infusion of 25, 50, 100, or 200 mg of RDZ (6 per dose group) or placebo (2 per dose group) either once (32 subjects) or once daily for 14 days (32 subjects). PK parameters were calculated from plasma and urinary concentrations using noncompartmental methods.

Results
For RDZ single doses, mean AUC_{0-t} values were 4.4, 9.4, 18.7, and 40.4 µg•h/mL and mean C_{max} values were 1.2, 2.5, 5.3, and 12.7 µg/mL for doses of 25, 50, 100, and 200 mg, respectively. For multiple doses, dose proportionality of AUC (P>0.05) of RDZ was determined for 25 to 200 mg, while C_{max} showed a statistically significant increase slightly greater than dose proportional (P<0.01) on Days 1 and 14. For multiple-dose PK, mean R_{ac} values were between 1.02 and 1.12. The mean renal clearance for all doses on Days 1 and 14 ranged from 1.38 to 2.27 L/h. The mean fraction of the administered dose excreted in urine at Day 14 ranged from 28.7% to 42.5%. In single dose groups, 2 subjects each reported at least 1 adverse event (AE) in both the 100, 200 mg (33.3%) RDZ, and placebo (25.0%) dose groups. No AEs were reported in the 25 or 50 mg RDZ groups. AEs in multiple dose groups were 66.7% to 83.3% for 25, 50, and 200 mg of RDZ, 33.3% for 100 mg RDZ, and 62.5% for placebo. The most common AEs for RDZ and placebo groups were gastrointestinal or administration site conditions. AEs were mild in severity, resolved by study end, and none led to study discontinuation.

Conclusion
The IV formulation of RDZ was well tolerated in healthy subjects and approximately dose proportional in single or multiple daily doses up to 14 days.

Introduction

RDZ is a novel oxazolidinone (Figure 1) being developed by Rib-X Pharmaceuticals, Inc. It has activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) has demonstrated clinical efficacy in community-acquired pneumonia (CAP) and complicated skin and skin structure infections (cSSSI) when administered as an oral product (1-2).

This Phase 1 study is part of the development program for an intravenous (IV) formulation of RDZ and evaluated the safety, tolerability, and pharmacokinetics of single- and multiple day (for 14 days) IV doses of RDZ or placebo at doses of 25, 50, 100, and 200 mg. This information will ultimately be used to help establish the doses and dosage regimen suitable for administration to subjects in future Phase 2 clinical studies.

Methods

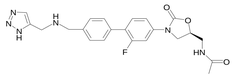
This was a randomized, double-blind, placebo-controlled, single-center study to evaluate the safety and pharmacokinetics of an IV formulation of RDZ administered as a single dose (Part 1) or once daily for 14 days (Part 2). Blinded safety data were reviewed by the sponsor and principal investigator before progression to the next higher dose group. Dosing in the next higher dose group was permitted only after the review of blinded safety data suggested that it was safe to do so. The first multiple day, ascending dose group (25 mg) began after completion of the first 2 (25 and 50 mg) single ascending dose groups. Blinded pharmacokinetic PK data from Part 1 were reviewed before dosing in Part 2. A total of 64 male and female subjects 18 to 65 years of age (inclusive) were randomly assigned to 1 of 4 treatment groups each within Parts 1 and 2 of the study (32 subjects in each part of the study). Each group consisted of 8 subjects each (6 active and 2 placebo). All doses were administered as a 1-hour continuous IV infusion. Subjects were screened within 28 days before the first infusion and checked into the clinic on Day –1 before dosing on Day 1. Subjects were confined in the clinic for a total of 4 nights for Part 1 and for 15 nights for Part 2. Each subject returned to the clinic for a follow-up visit approximately 5 days after Check-out.

In Part 1, on Day 1 subjects received a single infusion of either RDZ (25, 50, 100, or 200 mg) or placebo in an ascending fashion according to the randomization schedule. There was a minimum of 7 days between dose groups. In Part 2 on Days 1 through 14, subjects received a single infusion of either RDZ (25, 50, 100, or 200 mg) or placebo once daily in an ascending fashion according to the randomization schedule. There was a minimum of 10 days between dose groups in Part 2. PK sampling and safety assessments were performed according to the study schedule (Table 1).

Table 1. Schedule of Events for Part 1 and 2

	Screening	Check-in	Treatment Period Part 1/Part 2	Check-out Part 1/Part 2	Follow-up Part 1/Part 2
Study Day	**–28 to –1**	**–1**	**1 / 1 - 14**	**4 / 15**	**9 (± 2 days) / 20 (± 2 days)**
Informed consent	X				
Medical history	X	X			
12-Lead electrocardiogram	X	X	X	X	X
Urine drug and alcohol screen	X	X			
HBsAg, HCV, and HIV-1 and HIV-2 tests	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
Study drug administration			X		
PK sample collection			X	X	
Adverse event monitoring		X	X	X	X
Concomitant medications		X	X	X	X

Figure 1. Structure of RDZ



Results

Table 2a. Summary of Subject Disposition (All Subjects) - Part 1

Total number of subjects, n (%)	Treatment					Overall (N = 32)
	Placebo (Single Dose) (n = 8)	Dose Level of RDZ (Single, 1-Hour IV Infusion)				
		25 mg (n = 6)	50 mg (n = 6)	100 mg (n = 6)	200 mg (n = 6)	
Completed	8 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	32 (100.0)
Discontinued	0	0	0	0	0	0
Safety population	8 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	32 (100.0)
PK population	0	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	24 (75.0)

Abbreviation: IV, intravenous.
Note: Percentages were based on the number of subjects enrolled in each treatment for the safety population row, and were based on the number of subjects in the safety population for all other rows.

Table 2b. Summary of Subject Disposition (All Subjects) - Part 2

Total number of subjects, n (%)	Treatment					Overall (N = 32)
	Placebo (Multiple Dose) (n = 8)	Dose Level of RDZ (Multiple, 1-Hour IV Infusion)				
		25 mg (n = 6)	50 mg (n = 6)	100 mg (n = 6)	200 mg (n = 6)	
Completed	8 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	32 (100.0)
Discontinued	0	0	0	0	0	0
Safety Population	8 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	32 (100.0)
PK Population	0	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	24 (75.0)

Abbreviation: IV, intravenous.
Note: Percentages were based on the number of subjects enrolled in each treatment for the safety population row, and were based on the number of subjects in the safety population for all other rows.

Table 3a. Summary of Demographic and Baseline Characteristics (Safety Population) - Part 1

	Treatment					Overall (N = 32)
	Placebo (Single Dose) (n = 8)	Dose Level of RDZ (Single, 1-Hour IV Infusion)				
		25 mg (n = 6)	50 mg (n = 6)	100 mg (n = 6)	200 mg (n = 6)	
Mean Age in years (SD)	30.1 (8.74)	31.5 (9.61)	33.8 (13.64)	25.5 (3.15)	26.5 (11.64)	29.5 (9.75)
Male, n (%)	6 (75.0)	3 (50.0)	5 (83.3)	4 (66.7)	3 (50.0)	21 (65.6)
Female, n(%)	2 (25.0)	3 (50.0)	1 (16.7)	2 (33.3)	3 (50.0)	11 (34.4)
White, n(%)	4 (50.0)	4 (66.7)	5 (83.3)	5 (83.3)	6 (100.0)	24 (75.0)
Black or African American, n(%)	3 (37.5)	2 (33.3)	1 (16.7)	1 (16.7)	0	7 (21.9)
Asian, n(%)	1 (12.5)	0	0	0	0	1 (3.1)
Hispanic or Latino, n(%)	0	0	1 (16.7)	2 (33.3)	4 (66.7)	7 (21.9)
Not Hispanic or Latino, n(%)	8 (100.0)	6 (100.0)	5 (83.3)	4 (66.7)	2 (33.3)	25 (78.1)
Mean Height in cm (SD)	171.00 (7.14)	169.88 (11.23)	173.78 (9.12)	174.35 (10.87)	170.60 (9.57)	171.87 (9.07)
Mean Weight in kg (SD)	74.20 (10.13)	76.18 (7.70)	82.78 (6.13)	74.98 (15.99)	74.28 (14.15)	76.34 (11.08)
Mean BMI in kg/m^2 (SD)	25.33 (2.62)	26.47 (2.38)	27.63 (3.57)	24.52 (3.37)	25.38 (3.68)	25.83 (3.11)

Abbreviation: IV, intravenous, BMI, body mass index; SD, standard deviation
Note: Percentages were based on the number of subjects in the safety population who received the specified treatment and overall.

Table 3b. Summary of Demographic and Baseline Characteristics (Safety Population) - Part 2

	Treatment					Overall (N = 32)
	Placebo (Multiple Dose) (n = 8)	Dose Level of RDZ (Multiple, 1-Hour IV Infusion)				
		25 mg (n = 6)	50 mg (n = 6)	100 mg (n = 6)	200 mg (n = 6)	
Mean Age in years (SD)	39.1 (10.86)	40.0 (9.01)	28.5 (6.28)	29.8 (10.21)	37.8 (9.79)	35.3 (10.12)
Male, n (%)	3 (37.5)	4 (66.7)	5 (83.3)	4 (66.7)	5 (83.3)	21 (65.6)
Female, n (%)	5 (62.5)	2 (33.3)	1 (16.7)	2 (33.3)	1 (16.7)	11 (34.4)
White, n (%)	4 (50.0)	5 (83.3)	4 (66.7)	4 (66.7)	4 (66.7)	21 (65.6)
Black or African American, n (%)	4 (50.0)	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	10 (31.3)
Asian, n (%)	0	0	1 (16.7)	0	0	1 (3.1)
Hispanic or Latino, n (%)	3 (37.5)	2 (33.3)	2 (33.3)	1 (16.7)	0	8 (25.0)
Not Hispanic or Latino, n (%)	5 (62.5)	4 (66.7)	4 (66.7)	5 (83.3)	6 (100.0)	24 (75.0)
Mean Height in cm (SD)	166.46 (11.67)	171.18 (11.62)	172.57 (10.02)	169.97 (6.73)	174.82 (11.45)	170.72 (10.29)
Mean Weight in kg (SD)	71.33 (17.72)	75.45 (13.44)	72.83 (10.18)	67.58 (11.83)	75.12 (13.85)	72.39 (13.36)
Mean BMI in kg/m^2 (SD)	25.49 (4.07)	25.68 (3.31)	24.50 (3.01)	23.42 (3.95)	24.35 (2.19)	24.74 (3.31)

Abbreviation: IV, intravenous; BMI, body mass index; SD, standard deviation
Note: Percentages were based on the number of subjects in the safety population who received the specified treatment and overall.

Table 4a. Summary of Treatment-Emergent Adverse Events (Safety Population) – Part 1

System Organ Class Preferred Term	Treatment (Single, 1-Hour IV Infusion)					Overall (N = 32)
	Placebo (n = 8)	RDZ				
		25 mg (n = 6)	50 mg (n = 6)	100 mg (n = 6)	200 mg (n = 6)	
Total number of TEAEs	3	0	0	4	3	10
Subjects with at least 1 TEAE, n (%)	2 (25.0)	0	0	2 (33.3)	2 (33.3)	6 (18.8)
Subjects with at least 1 TEAE, n (%)						
Unrelated	0	0	0	0	0	0
Unlikely related	1 (12.5)	0	0	1 (16.7)	0	2 (6.3)
Possibly related	1 (12.5)	0	0	1 (16.7)	2 (33.3)	4 (12.5)
Probably related	0	0	0	0	0	0
Very likely/certainly related	0	0	0	0	0	0
Gastrointestinal disorders	1 (12.5)	0	0	1 (16.7)	1 (16.7)	3 (9.4)
General disorders and administration site conditions	0	0	0	1 (16.7)	1 (16.7)	2 (6.3)

Abbreviation: TEAE, treatment-emergent adverse event.
Note: The total number of adverse events counts all TEAEs for subjects in the safety population. Subjects could 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/she reported 1 or more events. Treatment-emergent adverse events were summarized by treatment at onset of the event. Percentages were based on the number of subjects in the safety population who received the specified treatment and overall.

Table 4b. Summary of Treatment-Emergent Adverse Events (Safety Population) – Part 2

System Organ Class Preferred Term	Treatment (Multiple, 1-Hour IV Infusion)					Overall (N = 32)
	Placebo (n = 8)	RDZ				
		25 mg (n = 6)	50 mg (n = 6)	100 mg (n = 6)	200 mg (n = 6)	
Total number of TEAEs	10	11	16	2	15	54
Number of subjects with at least 1 TEAE	5 (62.5)	4 (66.7)	4 (66.7)	2 (33.3)	5 (83.3)	20 (62.5)
Subjects with at least 1 TEAE, n (%)						
Unrelated	2 (25.0)	2 (33.3)	0	2 (33.3)	0	6 (18.8)
Unlikely	1 (12.5)	1 (16.7)	0	0	0	2 (6.3)
Possibly related	2 (25.0)	1 (16.7)	4 (66.7)	0	5 (83.3)	12 (37.5)
Probably related	0	0	0	0	0	0
Very likely/certainly related	0	0	0	0	0	0
General disorders and administration site conditions	1 (12.5)	3 (50.0)	4 (66.7)	2 (33.3)	5 (83.3)	15 (46.9)
Infusion site pain	1 (12.5)	2 (33.3)	4 (66.7)	2 (33.3)	5 (83.3)	14 (43.8)
Nervous system disorders	2 (25.0)	2 (33.3)	1 (16.7)	0	2 (33.3)	7 (21.9)
Headache	1 (12.5)	1 (16.7)	0	0	1 (16.7)	3 (9.4)
Gastrointestinal disorders	2 (25.0)	1 (16.7)	0	0	2 (33.3)	5 (15.6)
Abdominal pain	1 (12.5)	1 (16.7)	0	0	0	2 (6.3)
Diarrhoea	1 (12.5)	1 (16.7)	0	0	0	2 (6.3)
Nausea	0	1 (16.7)	0	0	1 (16.7)	2 (6.3)
Skin and subcutaneous tissue disorders	1 (12.5)	0	0	0	1 (16.7)	2 (6.3)

Results

Table 5a. Mean (%CV) Plasma and Urinary PK Parameters of RDZ (PK Population) - Part 1

Parameter (unit)	Treatment (Single, 1-Hour IV Infusion)			
	RDZ			
	25 mg (n=6)	50 mg (n=6)	100 mg (n=6)	200 mg (n=6)
Plasma Parameters				
AUC_{0-t} (µg•h/mL)	4.34 (9)	9.27 (13)	18.58 (6)	40.24 (5)
$AUC_{0-\infty}$ (µg•h/mL)	4.44 (9)	9.40 (12)	18.71 (6)	40.42 (5)
C_{max} (µg/mL)	1.19 (20)	2.53 (12)	5.34 (17)	12.70 (8)
T_{max} (h)[a]	1.00 (1.00, 1.02)	1.00 (1.00, 1.05)	1.01 (1.00, 1.08)	1.00 (1.00, 1.02)
$t_{1/2}$ (h)	5.05 (22)	6.05 (10)	5.88 (9)	9.93 (37)
CL (L/h)	5.66 (9)	5.38 (11)	5.36 (6)	4.96 (5)
V_z (L)	41.31 (23)	46.72 (11)	45.48 (10)	70.36 (34)
V_{ss} (L)	27.42 (18)	28.16 (11)	27.32 (15)	25.37 (16)
Urine Parameters				
Fe %$_{0-72}$ (%)	34.0 (26)	33.2 (23)	37.3 (24)	44.5 (19)
CL_r (L/h)	1.98 (30)	1.82 (29)	2.02 (25)	2.22 (18)

Abbreviations: CV, coefficient of variation; IV, intravenous.
[a]Median (minimum, maximum).

Table 5b. Mean (%CV) Plasma and Urinary PK Parameters of RDZ (PK Population) - Part 2

Parameter (unit)	Treatment (Multiple, 1-Hour IV Infusion)			
	RDZ			
	25 mg (n=6)	50 mg (n=6)	100 mg (n=6)	200 mg (n=6)
Day 1				
AUC_{0-t} (µg•h/mL)	4.61 (7)	9.69 (13)	20.96 (10)	39.84 (20)
C_{max} (µg/mL)	1.20 (14)	2.81 (9)	6.54 (7)	12.15 (19)
T_{max} (h)[a]	1.00 (1.00,1.02)	1.00 (1.00,1.05)	1.00 (1.00,1.05)	1.00 (1.00,1.00)
$t_{1/2}$ (h)	5.26 (23)	4.69 (14)	5.14 (9)	5.49 (6)
CL (L/h)	5.28 (8)	5.13 (14)	4.70 (11)	5.02 (18)
V_{ss} (L)	28.61 (20)	24.18 (9)	22.08 (12)	25.56 (22)
MRT (h)	5.47 (23)	4.75 (10)	4.70 (6)	5.08 (12)
Fe %$_{0-24}$ (%)	36.2 (6)	42.8 (19)	37.1 (17)	33.3 (32)
CL_r (L/h)	1.98 (11)	2.25 (28)	1.78 (17)	1.70 (34)
Day 14				
AUC_{0-t} (µg•h/mL)	5.17 (11)	9.90 (16)	22.77 (10)	43.53 (18)
C_{max} (µg/mL)	1.25 (15)	2.66 (16)	6.78 (9)	12.95 (20)
T_{max} (h)[a]	1.00 (1.00, 1.05)	1.00 (1.00, 1.08)	1.00 (1.00, 1.10)	1.00 (1.00, 1.05)
CL (L/h)	4.88 (10)	5.16 (16)	4.43 (10)	4.70 (15)
R_{ac}	1.12 (5)	1.02 (6)	1.09 (5)	1.10 (5)
Fe %$_{0-24}$ (%)	35.1 (30)	42.5 (34)	35.0 (20)	28.7 (36)
CL_r (L/h)	1.69 (28)	2.27 (46)	1.54 (20)	1.38 (45)

Abbreviations: CV, coefficient of variation; IV, intravenous.
[a]Median (minimum, maximum).

Figure 2a. Mean (± SD) Plasma Concentrations of RDZ Versus Time by Treatment (PK Population) - Part 1

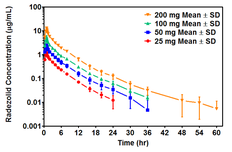
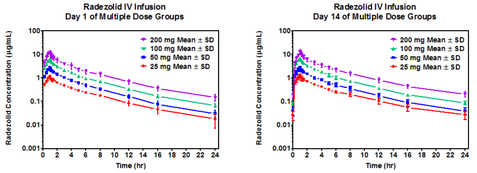


Table 6. Analysis of Dose Proportionality of RDZ (PK Population) - Part 2

Day	Parameter	Estimated Slope for Ln(Dose)	90% Confidence Interval for the Slope	P value (Slope=1)
1	AUC_{0-t} (µg•h/mL)	1.039	0.968 – 1.111	0.264
	$AUC_{0-\infty}$ (µg•h/mL)	1.041	0.969 – 1.113	0.247
	AUC_{0-tau} (µg•h/mL)	1.038	0.966 – 1.111	0.285
	C_{max} (µg/mL)	1.121	1.044 – 1.198	0.004
14	AUC_{0-t} (µg•h/mL)	1.040	0.964 – 1.115	0.285
	C_{max} (µg/mL)	1.144	1.057 – 1.231	0.002

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

Figure 2b. Mean (± SD) Plasma Concentrations of RDZ Versus Time by Treatment (PK Population) - Part 2



Conclusions

- Single and multiple (over 14 days) 1-hour IV infusions of RDZ at doses of 25, 50, 100, and 200 mg were safe and well tolerated by the healthy subjects in this study.
- The most frequently reported TEAE was infusion site pain, reported by 5 subjects after receiving 200 mg RDZ, 4 subjects after receiving 50 mg RDZ, and 2 subjects each after receiving 25 and 100 mg RDZ. One subject reported infusion site pain after receiving placebo.
- The majority of TEAEs were mild except 1 moderate TEAE of vomiting in the 200-mg RDZ treatment group that was considered unlikely related to study drug.
- There were no apparent treatment- or dose-related trends in clinical laboratory assessments, vital sign measurements, ECG results, or physical examination findings in either Part 1 or 2.
- RDZ was dose proportional with respect to the total exposure (AUC) parameters across the full range of doses (25 to 200 mg) in this study.
- RDZ showed a small but statistically significantly greater than dose-proportional increase for peak exposure (C_{max}) when evaluated across the full dose range.
- There was minimal accumulation of RDZ after dosing once daily for 14 days as indicated by the approximate increase in exposure from 2% to 12% on Day 14 compared with Day 1.

References

1. Lawrence, L, Danese P, DeVito, J, Franceschi, F, and Sutcliffe, J. In vitro activities of the Rx-01 Oxazolidinones against Hospital and Community Pathogens. Antimicrob Agents Chemother 2003; 47:3260-3269.
2. Eric Burak, Scott Hopkins, Chris Pillar, Nina Brown and Laura Lawrence. *In vitro* activity of radezolid against methicillin-resistant S. aureus causing skin and wound infections from the United States, Europe and Asia. 49th ICAAC, San Francisco, September, 2009.