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Acute Hemodynamic Effects of Riociguat in Patients With Pulmonary Hypertension Associated With Diastolic Heart Failure (DILATE-1)

A Randomized, Double-Blind, Placebo-Controlled, Single-Dose Study

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CHEST 2014; 146(5):1274–1285

e-Appendix 1.

Supplemental methods

Inclusion and exclusion criteria

Inclusion criteria included: signs or symptoms of heart failure; echocardiographic confirmation of preserved left ventricular ejection fraction (LVEF) > 50%; echocardiographic confirmation of preserved ejection fraction with LVEF > 50% and evidence for diastolic dysfunction, by either abnormal relaxation (E/A wave ratio < 1) or diastolic stiffness (E/A wave ratio > 2) in patients with sinus rhythm, or by E wave deceleration time < 150 ms in patients with atrial fibrillation; serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) > 220 pg/mL; and mean pulmonary artery pressure ≥ 25 mm Hg and pulmonary arterial wedge pressure > 15 mm Hg at rest. The main exclusion criteria were: pretreatment within 30 days of randomization with intravenous vasodilators, endothelin receptor antagonists, prostanoids, or phosphodiesterase-5 inhibitors; treatment within 7 days of randomization with nitric oxide donors; pulmonary hypertension of groups other than Dana Point Classification 2.2; systolic blood pressure >180 mm Hg or <95 mm Hg and /or diastolic blood pressure >110 mm Hg; significant coronary, carotid, or peripheral vascular disease. Patients with significant valvular heart disease were excluded.

Exploratory analysis of myocardial O_2 consumption

Myocardial O_2 (MVO_2) consumption was estimated with the Rooke-Feigl formula as MVO_2 = 0.000408*SBP*heart rate (HR)+0.000325*(0.8*SBP+0.2*DBP)*HR* stroke volume (SV)/Body weight+1.43.[1]

 DOI: 10.1378/chest.14-0106

Exploratory biomarker analysis

Serum NT-proBNP levels and the exploratory biomarkers galectin-3, procollagen type III, ST2, and asymmetric dimethylarginine were assessed at baseline, 8, and 24 h post-study drug administration.

Pharmacokinetic analysis

Plasma concentrations of riociguat were determined during the 24-h period following study drug administration using validated high performance liquid chromatography-mass spectrometry. The following parameters were calculated using WinNonlin Version 4.1 (Pharsight Corporation, Mountain View, CA, USA): area under the plasma concentration–time curve (AUC) from zero to infinity; AUC/dose; AUC divided by dose per kg body weight; peak plasma concentration (C_{max}); C_{max}/dose; time to reach maximum drug concentration in plasma (t_{max}); and half-life ($t_{1/2}$). *Adverse events*

AEs were defined as any event that started or worsened following administration of the single dose of study medication up until 2 days after administration.

The following adverse events were of special interest: decrease in invasively measured systemic systolic arterial blood pressure < 80 mm Hg or systemic mean arterial blood pressure < 60 mm Hg at any time during the study; decrease in cardiac output ≥ 20% of baseline; pulmonary edema; and syncope.

SUPPLEMENTAL REFERENCES

1. Rooke GA, Feigl EO. Work as a correlate of canine left ventricular oxygen consumption, and the problem of catecholamine oxygen wasting. Circ Res. 1982;50(2):273-286.

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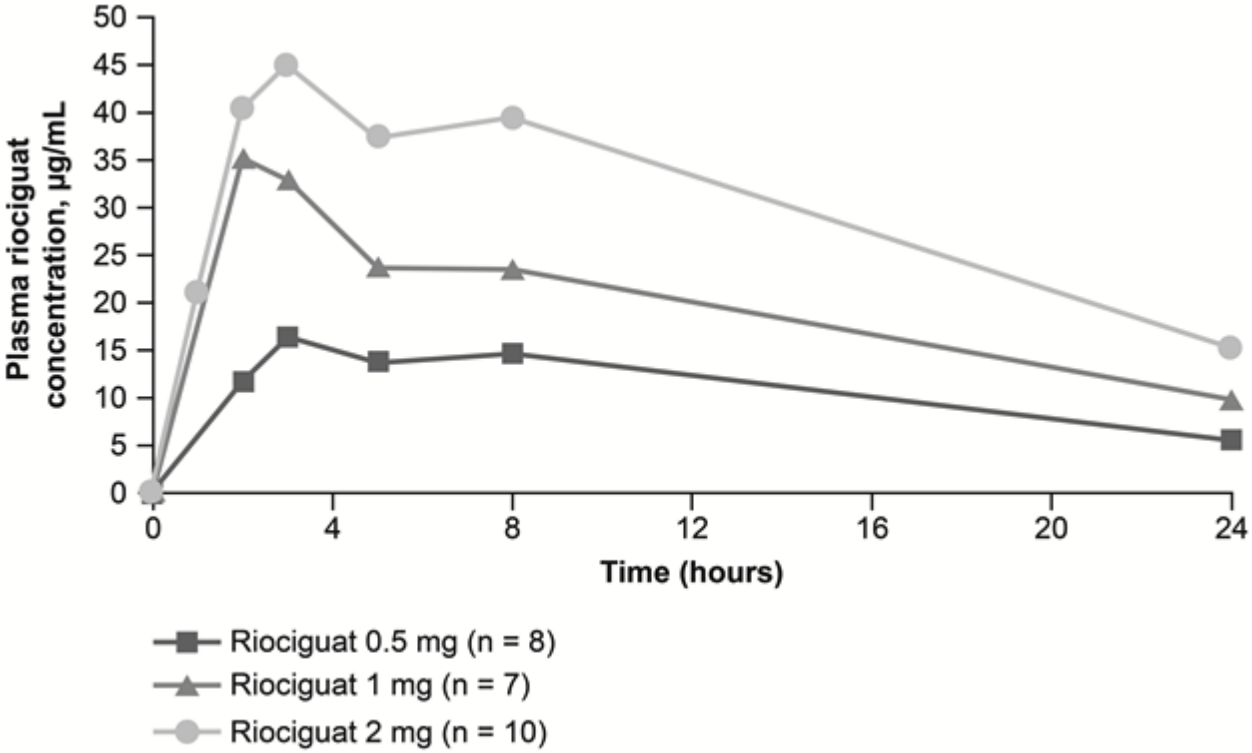
e-Figure 1. Geometric mean plasma concentration–time curves over 24 h following single doses of riociguat (0.5, 1, and 2 mg). Non-compartmental pharmacokinetic analyses were performed on plasma concentrations of riociguat.



e-Table 1—*Baseline Values (Standard Deviation) and Peak Changes from Baseline in Mean Pulmonary Artery Pressure*

Group	Baseline, mm Hg (SD)	Peak change from baseline, mm Hg (SD)	Difference vs placebo, mm Hg (SD)	*P*-value[a]
Placebo (n = 11)	34.9±8.0	–6.3±4.2	–	–
Riociguat 0.5 mg (n = 8)	32.0±4.5	–4.3±3.0	2.0±3.7	.3
Riociguat 1 mg (n = 7)	31.1±6.4	–2.4±5.7	3.8±4.8	.1
Riociguat 2 mg (n = 10)	35.1±8.8	–5.1±4.7	1.2±4.4	.6

[a]Two-group, two-sided *t* test.
SD = standard deviation.

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e-Table 2—*Changes (Least Squares Mean) from Baseline in Secondary Hemodynamic Parameters*

Parameter	Treatment	Change	Standard error	*P*-value[a]
Cardiac index, L/min/m^{-2}	Placebo	0.04	0.1	.6
	Riociguat 0.5 mg	0.1	0.1	.2
	Riociguat 1 mg	0.3	0.1	.007
	Riociguat 2 mg	0.5	0.1	<.0001
Cardiac output, L/min	Placebo	0.08	0.2	.7
	Riociguat 0.5 mg	0.3	0.2	.2
	Riociguat 1 mg	0.6	0.2	.01
	Riociguat 2 mg	1.0	0.2	<.0001
Diastolic blood pressure, mm Hg	Placebo	−2.4	1.9	.2
	Riociguat 0.5 mg	−2.4	2.2	.3
	Riociguat 1 mg	−5.8	2.4	.02
	Riociguat 2 mg	−8.7	2.0	.0001
Systolic blood pressure, mm Hg	Placebo	−2.1	3.6	.6
	Riociguat 0.5 mg	−2.8	4.3	.5
	Riociguat 1 mg	−16.3	4.6	.001
	Riociguat 2 mg	−13.7	3.8	.001
Heart rate, bpm	Placebo	2.3	2.3	.3
	Riociguat 0.5 mg	0.9	2.7	.7
	Riociguat 1 mg	−0.2	2.8	1.0
	Riociguat 2 mg	4.6	2.4	.06
Stroke volume, mL	Placebo	0.6	2.9	.8
	Riociguat 0.5 mg	5.2	3.4	.1
	Riociguat 1 mg	4.0	3.6	.3
	Riociguat 2 mg	9.4	3.0	.004
Stroke volume index, mL/m^2	Placebo	0.4	1.4	.8
	Riociguat 0.5 mg	2.6	1.7	.1
	Riociguat 1 mg	2.2	1.8	.2
	Riociguat 2 mg	4.6	1.5	.005
Systemic vascular resistance, dyn·s·cm $^{-5}$	Placebo	−90	82	.3
	Riociguat 0.5 mg	−113	97	.3
	Riociguat 1 mg	−366	103	.001
	Riociguat 2 mg	−336	86	.0005
Systemic vascular resistance index, dyn·s·cm^{-5}·m^2	Placebo	−170	153	.3
	Riociguat 0.5 mg	−229	179	.2
	Riociguat 1 mg	−691	191	.001
	Riociguat 2 mg	−624	160	.0005
Pulmonary vascular	Placebo	−4.6	21.0	.8
	Riociguat 0.5	−5.7	24.6	.8

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resistance, dyn·s·cm^{-5}	mg			
	Riociguat 1 mg	−28.2	26.3	.3
	Riociguat 2 mg	−20.8	22.0	.4
Pulmonary vascular resistance index, dyn·s·cm^{-5}·m^2	Placebo	−6.4	38.7	.9
	Riociguat 0.5 mg	−13.1	45.4	.8
	Riociguat 1 mg	−53.2	48.5	.3
	Riociguat 2 mg	−39.4	40.6	.3
Pulmonary arterial wedge pressure, mm Hg	Placebo	−2.8	0.9	.007
	Riociguat 0.5 mg	−1.7	1.1	.1
	Riociguat 1 mg	0.1	1.2	1.0
	Riociguat 2 mg	−2.9	1.0	.006
Right atrial pressure, mm Hg	Placebo	−0.9	1.0	.4
	Riociguat 0.5 mg	−0.7	1.2	.6
	Riociguat 1 mg	0.5	1.3	.7
	Riociguat 2 mg	−1.7	1.1	.1
Mean arterial pressure, mm Hg	Placebo	−4.3	2.5	.1
	Riociguat 0.5 mg	−4.1	3.0	.2
	Riociguat 1 mg	−9.3	3.2	.006
	Riociguat 2 mg	−12.3	2.6	<.0001
Mixed venous oxygen saturation, %	Placebo	1.2	1.5	.4
	Riociguat 0.5 mg	−1.1	1.7	.5
	Riociguat 1 mg	3.1	2.0	.1
	Riociguat 2 mg	2.5	1.6	.1
Transpulmonary pressure gradient, mm Hg	Placebo	−0.1	1.0	.9
	Riociguat 0.5 mg	0.4	1.2	.8
	Riociguat 1 mg	0.9	1.3	.5
	Riociguat 2 mg	0.7	1.1	.5

[a]Paired *t* test.

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e-Table 3—*Baseline Values (Standard Deviation) and Changes (Least Squares Mean) from Baseline in Post-hoc Hemodynamic Parameters*

Parameter (SD)	Placebo (n = 11)		Riociguat 0.5 mg (n = 8)		Riociguat 1 mg (n = 7)		Riociguat 2 mg (n = 10)		Treatment difference (95% CI)[a]	*P*-value[a]
	Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change		
Diastolic pressure gradient, mm Hg	3.4 ±3.2	1.2	2.1±4.1	1.0	1.1±3.0	3.0	1.3±2.4	2.5	1.3 (−1.6 to 4.2)	.4
Pulmonary arterial pulse pressure, mm Hg	29.8±14.2	2.3	28.0±8.6	1.1	29.4±16.6	−2.4	31.2±13.2	−1.9	−4.1 (−9.1 to 0.8)	.1
Systemic arterial pulse pressure, mm Hg	67.2±17.3	0.3	85.9±21.9	−0.4	83.7±15.3	−10.5[b]	82.9±21.9	−5.1	−5.4 (−14.3 to 3.5)	.2
Systemic arterial compliance, mL.mm Hg^{-1}	1.0±0.6	−0.01	1.0±0.2	0.06	0.9±0.4	0.2[c]	1.0±0.4	0.2	0.2 (0.02 to 0.4)	.03
Pulmonary arterial capacitance, mL.mm Hg^{-1}	2.7±1.9	−0.3	3.1±0.8	0.06	3.4±2.4	0.6	2.6±1.1	0.4	0.7 (−0.1 to 1.5)	.1
Right ventricular stroke work, g·m	22.6±20.2	−3.9	24.8±5.7	0.6	19.7±11.9	2.0	25.0±14.5	2.5	6.4 (−0.7 to 13.5)	.07

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Left ventricular stroke work, g·m	52.8±19.0	−1.4	72.3±16.7	1.3	72.5±39.4	−6.7	65.1±31.3	−3.9	−2.4 (−11.2 to 6.4)	.6
Myocardial O_2 consumption, mL/min	6.9±1.5	0.06	7.6±1.6	0	8.2±2.0	−0.5	7.8±1.5	−0.04	−0.1 (−0.9 to 0.7)	.8

[a]Riociguat 2 mg vs placebo.
[b]Treatment difference: −10.8 (95% CI: −20.7 to −1.0); *P* = .03.
[c]Treatment difference: 0.2 (95% CI: 0.02 to 0.4); *P* = .03.
The mean changes from baseline of all evaluations up to 6 h after study drug administration are shown.

 DOI: 10.1378/chest.14-0106

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e-Table 4—*Baseline-Adjusted Analysis of Changes (Least Squares Mean) in Selected Hemodynamic Parameters*

Parameter (SD)	Placebo (n = 11)		Riociguat 0.5 mg (n = 8)		Riociguat 1 mg (n = 7)		Riociguat 2 mg (n = 10)		Treatment difference (95% CI)[a]	*P*-value[a]
	Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change		
Stroke volume, mL	66.6±34.0	0.4	81.5±18.0	5.4	77.8±36.7	4.1	75.1±27.1	9.4	9.0 (0.4 to 17.7)	.04
Stroke volume index, mL/m^2	34.2±14.3	0.2	42.9±7.9	2.9	39.1±17.1	2.2	38.4±10.4	4.6	4.4 (0.1 to 8.7)	.04
Systemic vascular resistance, dyn·s·cm^{-5}	1583±689	−32	1246±392	−152	1352±795	−375	1294±481	−362	−329 (−524 to −135)	.002
Systemic arterial compliance, mL/mm Hg	1.0±0.6	0	1.0±0.2	0.1	0.9±0.4	0.2	1.0±0.4	0.2	0.2 (0.01 to 0.4)	.04
Cardiac output, L/min	4.2±1.9	0.1	5.0±0.7	0.3	5.2±1.9	0.6	4.9±1.5	1.0	0.9 (0.3 to 1.5)	.002
Cardiac index, L/min/m^2	2.2±0.8	0	2.7±0.5	0.2	2.6±0.9	0.3	2.5±0.5	0.5	0.5 (0.2 to 0.7)	.0003
Filling resistance, mm Hg/(L/min)	5.5±2.3	−0.7	3.8±0.7	−0.8	4.9±4.0	−0.7	4.7±1.4	−1.3	−0.6 (−1.1 to −0.1)	.03
Systolic blood pressure, mm Hg	129.5 ±20.2	−4.0	143.3 ±19.3	−1.9	144.7 ±22.8	−15.2	141.6 ±24.9	−13.2	−9.2 (−19.7 to 1.2)	.08

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Diastolic blood pressure, mm Hg	62.3±11.9	−1.7	57.4±9.7	−3.2	61.0±10.2	−5.5	58.7±11.2	−9.1	−7.4 (−12.1 to −2.7)	.003
Mean arterial pressure, mm Hg	83.9±15.9	−4.7	85.0±11.9	−4.1	86.0±13.1	−9.0	85.6±14.8	−12.1	−7.5 (−13.8 to −1.2)	.02

[a]Riociguat 2 mg vs placebo.
The mean changes from baseline of all evaluations up to 6 h after study drug administration are shown.

 DOI: 10.1378/chest.14-0106

e-Table 5—*Baseline Values (Standard Deviation) and Changes (Least Squares Mean) from Baseline in Echocardiographic Parameters*

Parameter (SD)	Placebo			Riociguat 0.5 mg			Riociguat 1 mg			Riociguat 2 mg			Treatment difference (95% CI)[a]	*P*-value[a]
	n	BL	Change	n	BL	Change	n	BL	Change	n	BL	Change		
Left ventricular end-diastolic volume, mL	10	77.9 ±38.4	2.1	7	99.0 ±33.9	−13.0	6	94.7 ±20.7	1.4	10	99.2 ±39.4	−5.7	−7.8 (−22.9 to 7.4)	.3
Left ventricular end-diastolic volume index, mL/m^2	10	40.9 ±18.2	0.7	7	49.9 ±14.5	−6.4	6	48.1 ±8.0	0.01	10	50.8 ±16.5	−3.3	−4.1 (−11.5 to 3.4)	.3
Left ventricular end-systolic volume, mL	10	29.7 ±16.3	3.8	7	41.7 ±16.6	−5.4	6	35.3 ±8.2	−0.1	10	35.0 ±14.0	−4.3	−8.0 (−17.5 to 1.4)	.09
Left ventricular ejection fraction, %	10	62.2 ±5.5	−3.0	7	57.8 ±8.3	0.5	6	62.8 ±1.3	0.1	10	64.5 ±8.5	2.3	5.3 (−1.7 to 12.3)	.1
Left atrial area, cm^2	11	23.7 ±5.8	1.7	7	26.3 ±5.9	−1.8	7	25.3 ±7.2	−0.9	10	26.6 ±6.4	−2.3	−4.0 (−8.1 to 0.1)	.06
Right ventricular end-diastolic area, cm^2	11	18.6 ±8.4	2.8	7	17.8 ±5.1	−0.8	5	25.3 ±10.8	−1.7	10	23.8 ±11.5	−2.8	−5.6 (−10.9 to −0.3)	.04

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Right ventricular end-systolic area, cm^2	11	14.3 ±8.7	−1.0	7	9.7 ±2.8	1.0	5	17.4 ±9.3	−2.7	10	15.0 ±9.7	1.9	2.8 (−2.2 to 7.9)	.3
Right atrial area, cm^2	11	23.4 ±5.1	1.1	7	23.4 ±6.2	−1.1	7	26.3 ±5.8	−4.9	10	24.9 ±3.7	0.4	−0.7 (−4.8 to 3.4)	.7
Systolic pulmonary arterial pressure, mm Hg	11	56.3 ±18.7	−0.5	7	57.6 ±10.6	−3.8	5	50.2 ±20.1	4.7	10	52.2 ±12.9	−1.1	−0.5 (−6.4 to 5.4)	.9
Tricuspid annular plane systolic excursion, mm	11	17.4 ±3.3	0.9	7	21.2 ±4.7	−0.3	5	17.6 ±4.5	−2.1	9	19.1 ±7.1	0.6	−0.2 (−2.6 to 2.1)	.8
Mitral peak velocity of early filling (rest), cm/s	7	104.8 ±37.4	3.6	6	118.0 ±58.7	0.8	4	71.3 ±29.4	11.0	8	105.0 ±16.5	−3.8	−7.4 (−23.2 to 8.3)	.3
Mitral peak velocity of late filling (rest)[b], cm/s	3	53.0 ±21.4	3.3	3	50.9 ±8.8	2.4	2	73.0 ±10.2	12.9	6	66.0 ±43.7	−2.1	−5.3 (−16.5 to 5.8)	.3
Mitral peak velocity of early filling/mitral peak velocity of late filling ratio (rest)[b]	3	2.0 ±1.2	−0.01	3	1.4 ±0.2	0.06	2	0.8 ±0.2	0.04	6	2.0 ±0.9	0.1	0.1 (−0.2 to 0.5)	.4

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E-wave deceleration time (rest), ms	11	153.6 ±53.4	23.1	6	158.7 ±31.3	16.4	5	154.5 ±42.4	5.1	7	176.6 ±69.1	−7.0	−30.1 (−70.2 to 10.0)	.1

[a]Riociguat 2 mg vs placebo.
[b]A only measured in patients with sinus rhythm.
The mean changes from baseline of all evaluations up to 6 h after study drug administration are shown.
BL = baseline.

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e-Table 6—*Baseline Values (Standard Deviation) and Changes (Least Squares Mean) from Baseline in Plasma Biomarkers*

	Placebo (n = 11)		Riociguat 0.5 mg (n = 8)		Riociguat 1 mg (n = 7)		Riociguat 2 mg (n = 10)		Treatment difference (95% CI)[a]	*P*-value[a]
Parameter (SD)	**Baseline**	**Change**	**Baseline**	**Change**	**Baseline**	**Change**	**Baseline**	**Change**		
NT-proBNP, pg/mL	2019 ±1383	−43	1422 ±1371	80	848±553	151	1976 ±2496	889	933 (−380 to 2245)	.2
Procollagen type III, U/mL	1.3±0.4[b]	0.01	1.4±0.4	0.1	1.2±0.5	0.1	1.1±0.3	0.2	0.2 (0.03 to 0.3)	.02
ADMA, µmol/L	0.56±0.14	0.01	0.48±0.08	0	0.74±0.08	−0.03	0.48±0.06	0	−0.02 (−0.08 to 0.04)	.6
ST2, ng/mL	21.5 ±16.8[b]	−0.3	18.3±7.0	0.7	14.4±4.3	6.4	26.9±18.2	2.8	3.1 (−5.5 to 11.6)	.5
Galectin-3, ng/mL	8.5±1.8[b]	0.1	9.2±4.0	0.1	6.8±2.3	−0.02	8.8±2.5	0.7	0.6 (−1.0 to 2.2)	.5

[a]Riociguat 2 mg vs placebo.
[b]n = 10.
The mean changes from baseline of the evaluations at 8 and 24 h after study drug administration are shown.
ADMA = asymmetric dimethylarginine; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

 DOI: 10.1378/chest.14-0106

e-Table 7—Pharmacokinetic Parameters of Riociguat

Parameter	Riociguat 0.5 mg (n = 8)			Riociguat 1 mg (n = 7)			Riociguat 2 mg (n = 10)		
	Geometric mean	CV (%)	Range	Geometric mean	CV (%)	Range	Geometric mean	CV (%)	Range
AUC, μg·h/L	396.2	86.9	98.8–859.7	689.2	102.0	188.7–3060.0	1041.7[a]	45.1	580.5–2507.9
AUC/D, H/L	0.8	86.9	0.2–1.7	0.7	102.0	0.2–3.1	0.5[a]	45.1	0.3–1.3
C_{max}, μg/L	21.7	36.8	13.0–37.4	40.1	55.7	18.8–74.7	69.0	37.4	42.2–123.7
C_{max}/D, L^{-1}	0.04	36.8	0.03–0.07	0.04	55.7	0.02–0.07	0.03	37.4	0.02–0.06
$t_{1/2}$, h	14.3	75.1	4.0–29.4	13.8	64.5	7.5–43.9	13.1[a]	35.9	7.5–19.6
t_{max}, h	2.5[b]	–	0.5–8.0	2.0[b]	–	0.6–2.9	1.9[b]	–	0.7–8.0

[a]n = 8.
[b]Median.
The geometric means (standard deviation) are shown.
AUC = area under the plasma concentration−time curve from zero to infinity; AUC/D = AUC/dose; AUC_{norm} = area under the plasma concentration−time curve divided by dose per kg body weight; C_{max} = peak plasma concentration; C_{max}/D = C_{max}/dose; CV = coefficient of variation; t_{max} = time to reach maximum drug concentration in plasma; $t_{1/2}$ = half-life.

 DOI: 10.1378/chest.14-0106