Supplemental Material for:
Added Benefit of Raxibacumab to Antibiotic Treatment of Inhalational Anthrax

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Supplemental Table S1 Demographic and baseline characteristics[a]

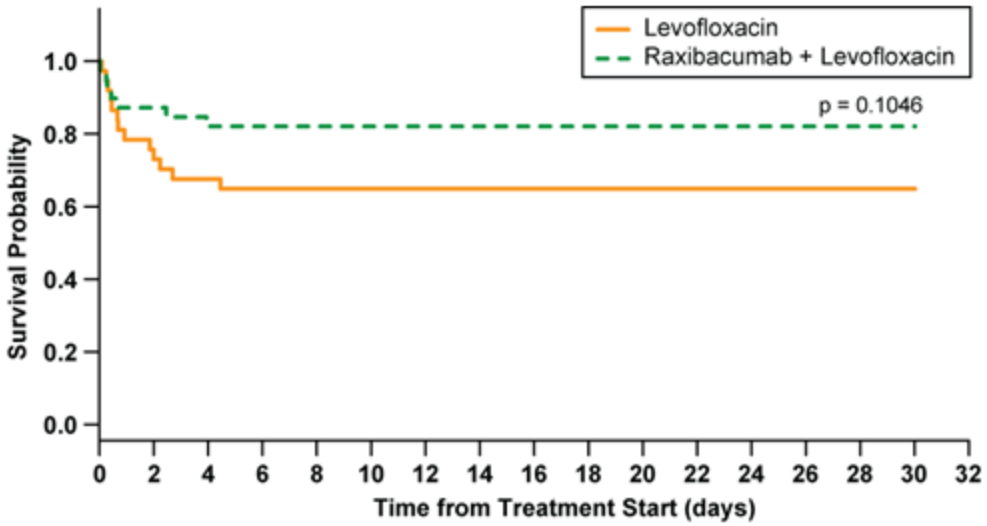
	Spore Challenged	Died before Treatment[b]	Levofloxacin (50 mg/kg qd x 3) + Placebo	Levofloxacin (50 mg/kg qd x 3) + Raxibacumab (40 mg/kg)	P-value[c]
N	180	104	37	39	
Sex					0.8276
Male	90 (50.0%)	54 (51.9%)	18 (48.6%)	18 (46.2%)	
Female	90 (50.0%)	50 (48.1%)	19 (51.4%)	21 (53.8%)	
Weight (kg)					0.7609
Mean ± SD	3.1 ± 0.2	3.2 ± 0.2	3.1 ± 0.2	3.1 ± 0.2	
Median	3.1	3.1	3.1	3.1	
(Minimum, Maximum)	(2.8, 3.9)	(2.8, 3.9)	(2.8, 3.5)	(2.8, 3.6)	
Age at randomization (months)					0.8727
Mean ± SD	7.5 ± 1.6	7.5 ± 1.6	7.4 ± 1.5	7.4 ± 1.5	
Median	6.7	7.0	6.7	6.7	
(Minimum, Maximum)	(6.0, 11.8)	(6.0, 11.8)	(6.0, 11.1)	(6.0, 10.9)	

[a] qd, once daily
[b] Challenged and died before treatment.
[c] P-value for comparison across 2 treatment groups obtained from likelihood ratio chi-square or Fisher's exact test for categorical data, and 1-way ANOVA for continuous data.

Supplemental Table S2 Incidence of bacteremia over time in surviving rabbits[a]

	Levofloxacin (50 mg/kg qd x 3) + Placebo N = 37		Levofloxacin (50 mg/kg qd x 3) + Raxibacumab (40 mg/kg) N = 39	
	Survivors (%)	Bacteremic (%)	Survivors (%)	Bacteremic (%)
Prior to treatment[b]	37 (100.0%)	37 (100.0%)	39 (100.0%)	38 (97.44%)
2 h post 1st LVX dose	36 (97.30%)	26 (72.22%)	38 (97.44%)	22 (57.89%)
24 h post 1st LVX dose	29 (78.38%)	0 (0.00%)	34 (87.18%)	2 (5.88%)
2 h post 2nd LVX dose	28 (75.68%)	1 (3.57%)	34 (87.18%)	0 (0.00%)
24 h post 2nd LVX dose	27 (72.97%)	0 (0.00%)	34 (87.18%)	0 (0.00%)
2 h post 3rd LVX dose	26 (70.27%)	1 (3.85%)	34 (87.18%)	0 (0.00%)
24 h post 3rd LVX dose	25 (67.57%)	0 (0.00%)	33 (84.62%)	0 (0.00%)
2 days post 3rd LVX dose	25 (67.57%)	0 (0.00%)	32 (82.05%)	0 (0.00%)
3 days post 3rd LVX dose	24 (64.86%)	1 (4.17%)	32 (82.05%)	0 (0.00%)
7 days post 3rd LVX dose	24 (64.86%)	0 (0.00%)	32 (82.05%)	0 (0.00%)

[a] qd, once daily; LVX, levofloxacin
[b] Positive for bacteremia at or prior to treatment.



Supplemental Figure S1 Survival time from treatment

P-value obtained from a log-rank test comparing survival time from treatment initiation between the raxibacumab/levofloxacin combination group and the levofloxacin alone group.

Supplemental Table S3 Immunogenicity (anti-raxibacumab antibodies)[a]

	Levofloxacin (50 mg/kg qd x 3) + Placebo N = 37		**Levofloxacin (50 mg/kg qd x 3) + Raxibacumab (40 mg/kg) N = 39**	
	Pre-treatment	**Day 28**	**Pre-treatment**	**Day 28**
Evaluable samples	37	24	39	32
Positive	3[1]	4	3[1]	23

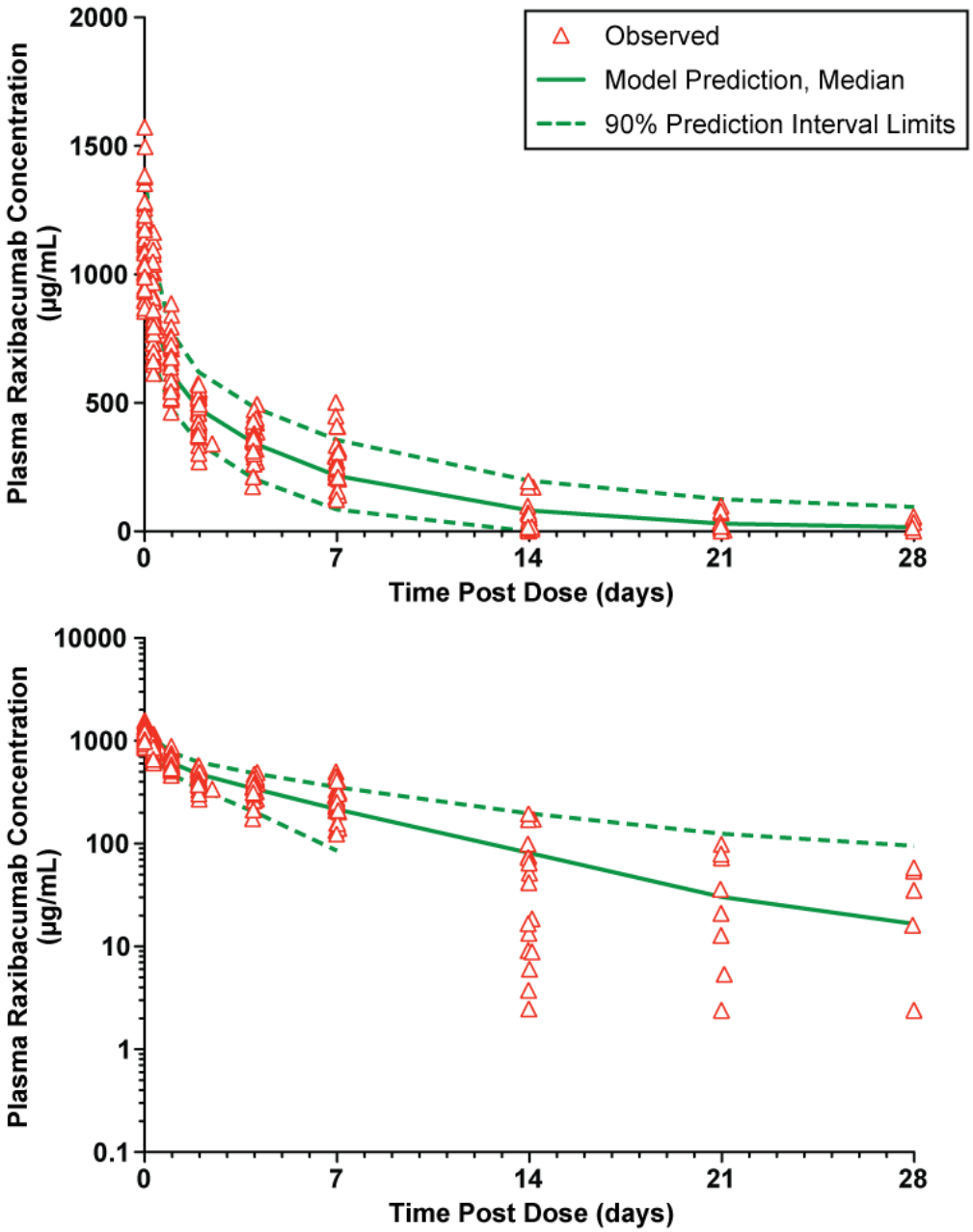
[a] qd, once daily

[b] These rabbits were also positive at Day 28.

Supplemental Table S4 TNA titers in surviving rabbits[a]

	Levofloxacin (50 mg/kg qd x 3) + Placebo N = 37		Levofloxacin (50 mg/kg qd x 3) + Raxibacumab (40 mg/kg) N = 39	
	Prechallenge	**Day 28**	**Prechallenge**	**Day 28**
n	24	24	32	32
Mean ± SD	0 ± 0	5150 ± 3495	0 ± 0	4741 ± 3005

[a] qd, once daily



Supplemental Figure S2 Visual predictive check for the raxibacumab pharmacokinetic model with individual observed plasma raxibacumab concentrations in rabbits administered 3 daily intragastric 50 mg/kg levofloxacin doses alone or in combination with a single intravenous 40 mg/kg raxibacumab dose

Upper panel, linear scale; lower panel, semilog scale. Lower bound of 90% prediction interval is zero at 14 days post dose and later.

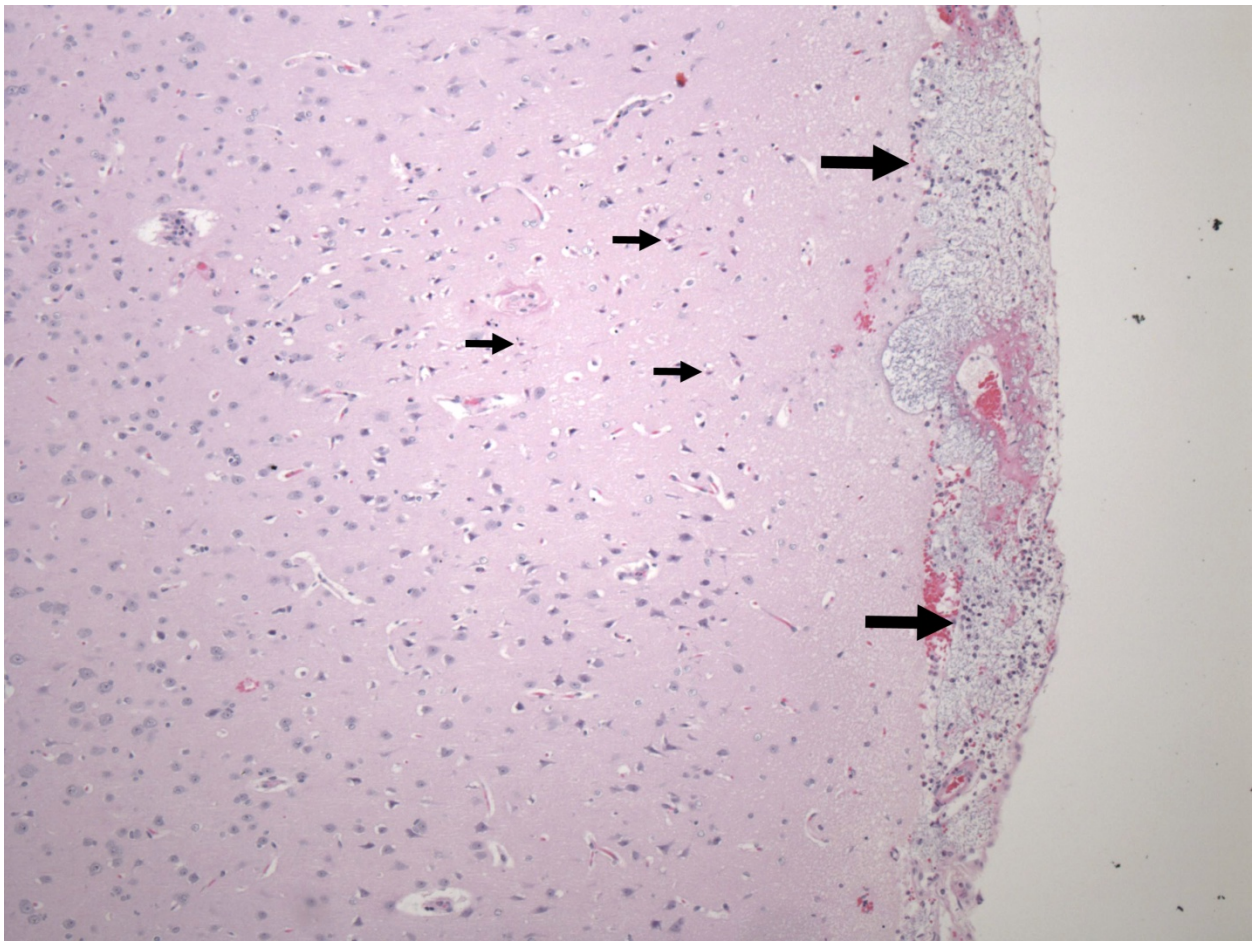
Supplemental Table S5 Incidence and mean severity of selected microscopic observations in non-surviving animals[a]

Tissue/Observation		Incidence (Mean Severity)[b] Levofloxacin (50 mg/kg qd x 3) + Placebo N = 13	Levofloxacin (50 mg/kg qd x 3) + Raxibacumab (40 mg/kg) N = 7
Brain	Number Examined	13	6
Bacteria, meninges		1 (0.2)	0 (0)
Hemorrhage(s)		2 (0.3)	0 (0)
Hemorrhage(s), Cerebellum		1 (0.1)	0 (0)
Hemorrhage(s), Cerebral Cortex, Fronto-Parietal		2 (0.2)	0 (0)
Hemorrhage(s), Cerebral Cortex, Temporo-Parietal		1 (0.1)	0 (0)
Hemorrhage(s), Meninges		1 (0.2)	0 (0)
Hemorrhage(s), Thalamus		1 (0.1)	0 (0)
Necrosis, Meningeal vascular		1 (0.2)	0 (0)
Necrosis, Parenchyma		1 (0.1)	0 (0)
Kidney	Number Examined	13	7
Tubular Atrophy		1 (0.2)	0 (0)
Liver	Number Examined	13	7
Necrosis, Hepatocellular		6 (0.7)	2 (0.6)
Sinusoidal Leukocytosis		2 (0.2)	1 (0.1)
Lung	Number Examined	13	7
Bacteria		2 (0.4)	[c]
Hemorrhage		5 (0.7)	2 (0.3)
Necrosis, BALT		4 (0.9)	1 (0.6)
Fibrin exudation, alveolar		4 (0.7)	2 (0.3)
Heterophilic inflammation		4 (0.7)	1 (0.3)
Lymph Node, Bronchial	Number Examined	13	7
Bacteria		2 (0.3)	0 (0)
Fibrin exudation		9 (1.6)	5 (2.3)
Hemorrhage(s)		8 (0.9)	5 (0.9)
Heterophilic inflammation		2 (0.3)	4 (0.9)
Necrosis, lymphoid		11 (2.6)	6 (2.6)
Lymph Node, Mediastinal	Number Examined	13	7
Bacteria		2 (0.5)	1 (0.3)
Fibrin exudation		8 (1.6)	5 (1.6)
Hemorrhage(s)		8 (1.2)	5 (1.1)
Heterophilic inflammation		1 (0.2)	3 (0.6)
Necrosis, lymphoid		11 (2.3)	5 (2.1)
Spleen	Number Examined	13	6
Bacteria		0 (0.0)	1 (0.2)
Fibrin exudation		4 (0.5)	3 (0.8)
Heterophilic inflammation		2 (0.2)	1 (0.3)
Necrosis, lymphoid		3 (0.6)	1 (0.3)

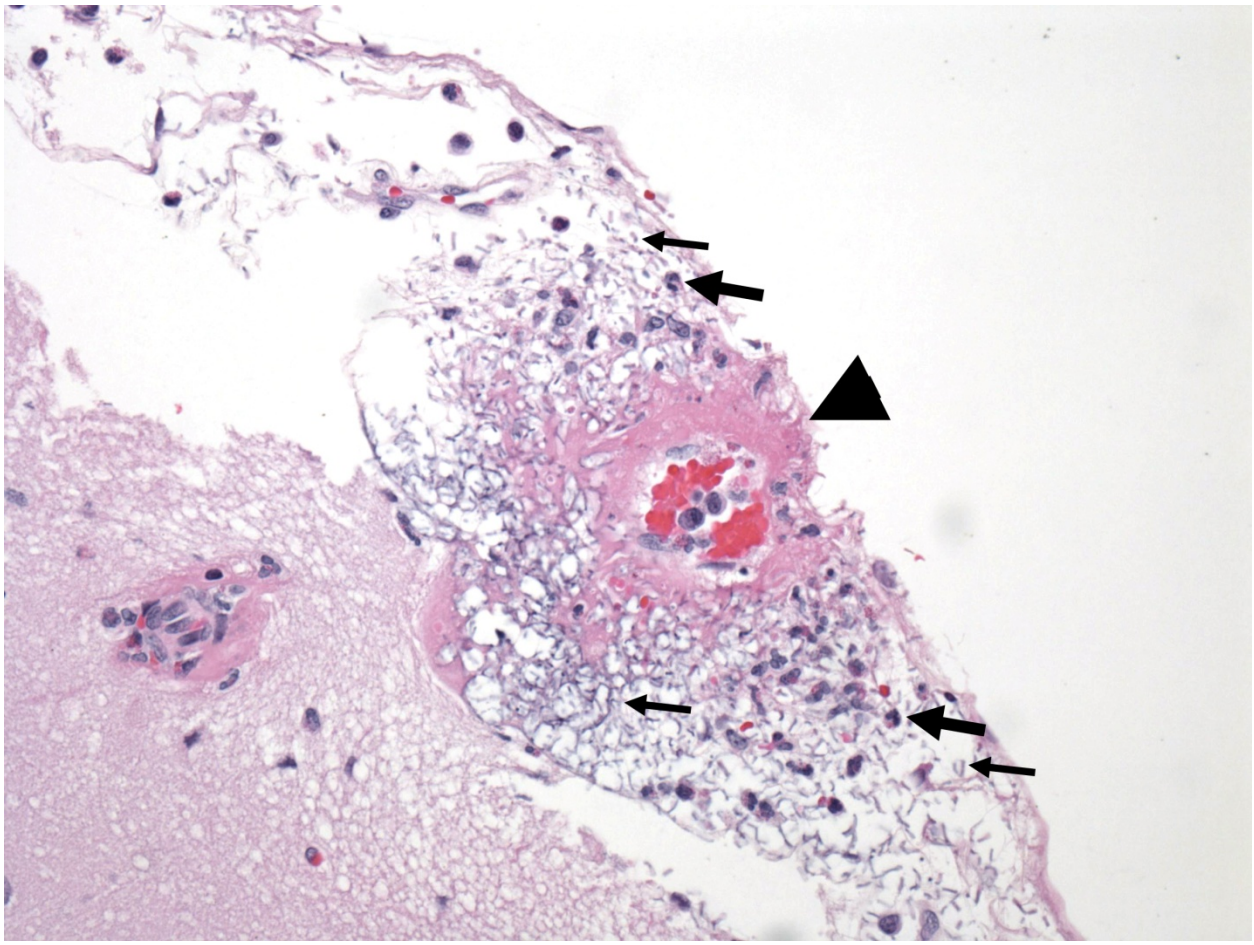
[a] qd, once daily

[b] All microscopic findings were graded semiquantitatively according to the following scale: minimal (Grade 1) represented the least detectible lesion; mild (Grade 2) represented an easily discernible lesion; moderate (Grade 3) represented a change affecting a large area of the represented tissue; and marked (Grade 4) represented a lesion that approached maximal.

[c] No value given.



Supplemental Figure S3 Cerebral cortex and meninges from animal L23083, a levofloxacin and buffer-treated monkey with meningeal vascular necrosis and associated parenchymal necrosis. Large arrows show numerous large rods characteristic of *Bacillus anthracis*, as well as frequent leukocytes. Small arrows show several necrotic neurons. 10X magnification, Haematoxylin and Eosin stain.



Supplemental Figure S4 A higher magnification of the meninges of animal L23083. The arrowhead indicates a small vessel with leakage of plasma proteins with an appearance consistent with fibrin (cerebral vascular necrosis). Large arrows indicate neutrophils and small arrows bacteria within the meninges. 40X magnification, Haematoxylin and Eosin stain.

Supplemental Table S6 Levofloxacin exposures for rabbits in the current study compared with exposures for humans administered 500 or 750 mg levofloxacin doses[a]

Levofloxacin Dosing	$C_{max,n}$ (µg/mL)	$C_{min,n}$ (µg/mL)
Rabbit, based on PK results from current study[b]		
1st Dose	6.2	0.4
2nd Dose	7.5	0.5
3rd Dose	7.0	0.8
Human, based on information provided in Levaquin® product labeling		
500 mg	5.7	0.5
750 mg	8.6	1.1

[a] $C_{max,n}$, maximum plasma levofloxacin concentration after the n^{th} dose, defined as the concentration measured 2 hours after the dose; $C_{min,n}$, minimum plasma levofloxacin concentration after the n^{th} dose, defined as the concentration measured just prior to the subsequent dose, or at 24 hours after the 3rd dose.

[b] Mean values for Group 2 (levofloxacin alone).