

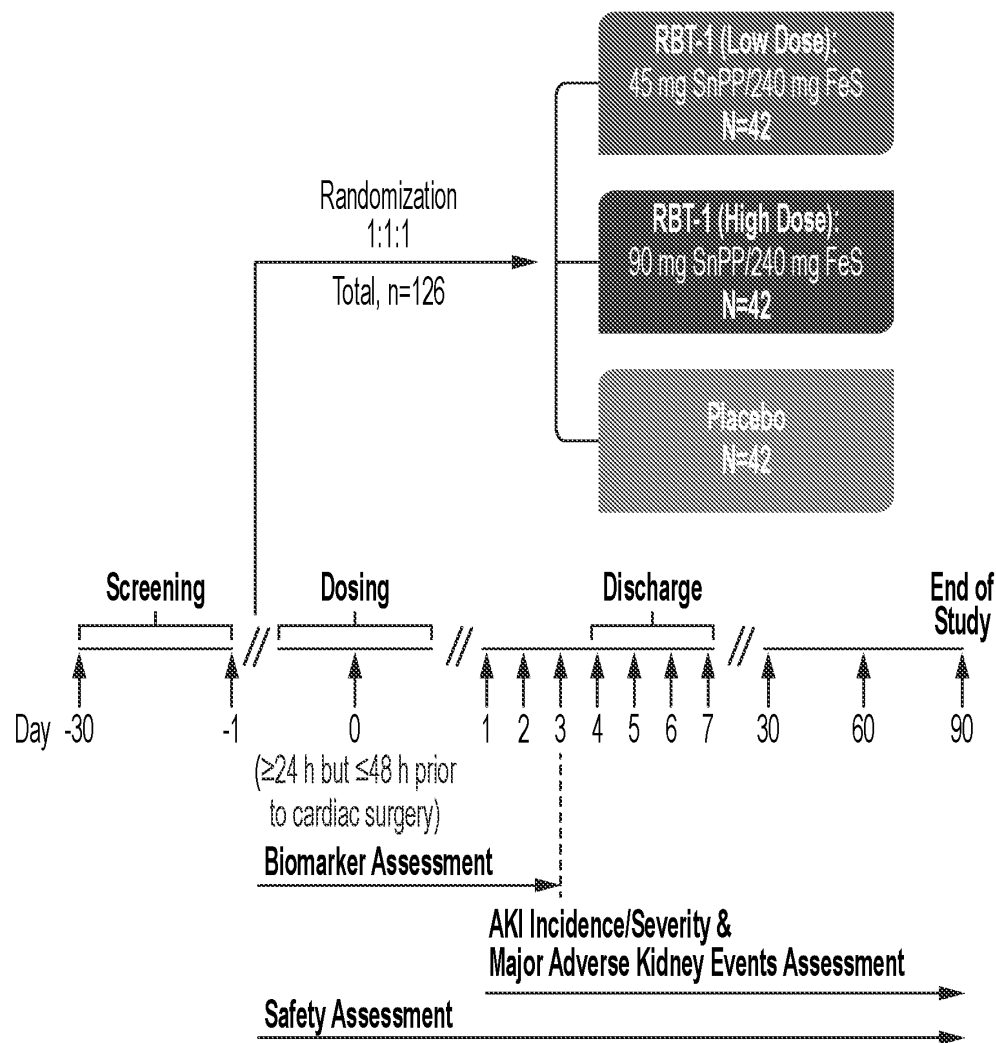


FIG. 1

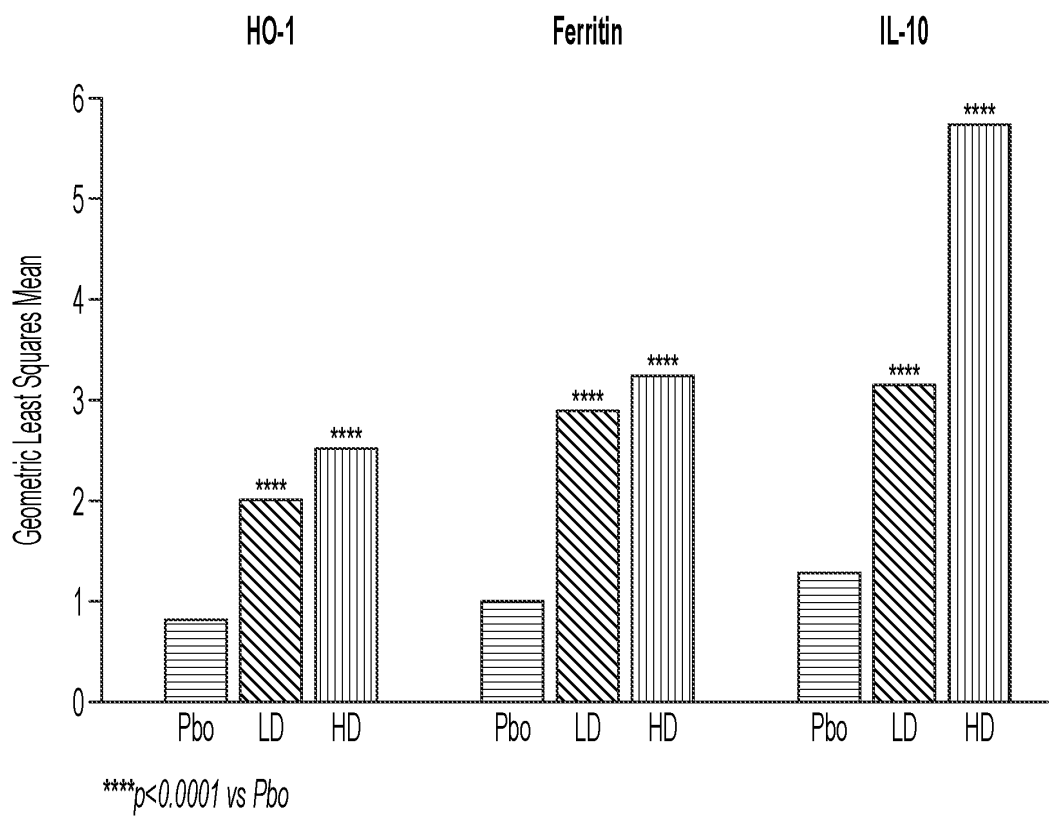


FIG. 2

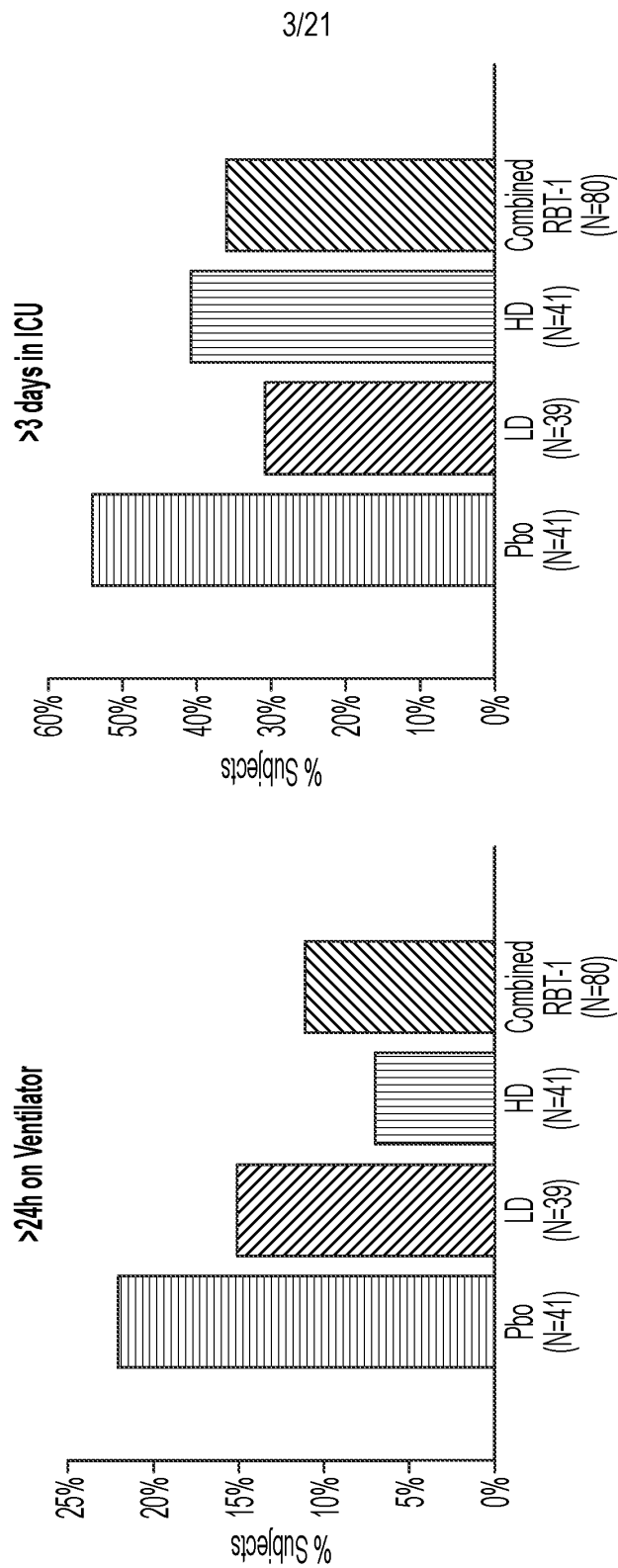


FIG. 3

4/21

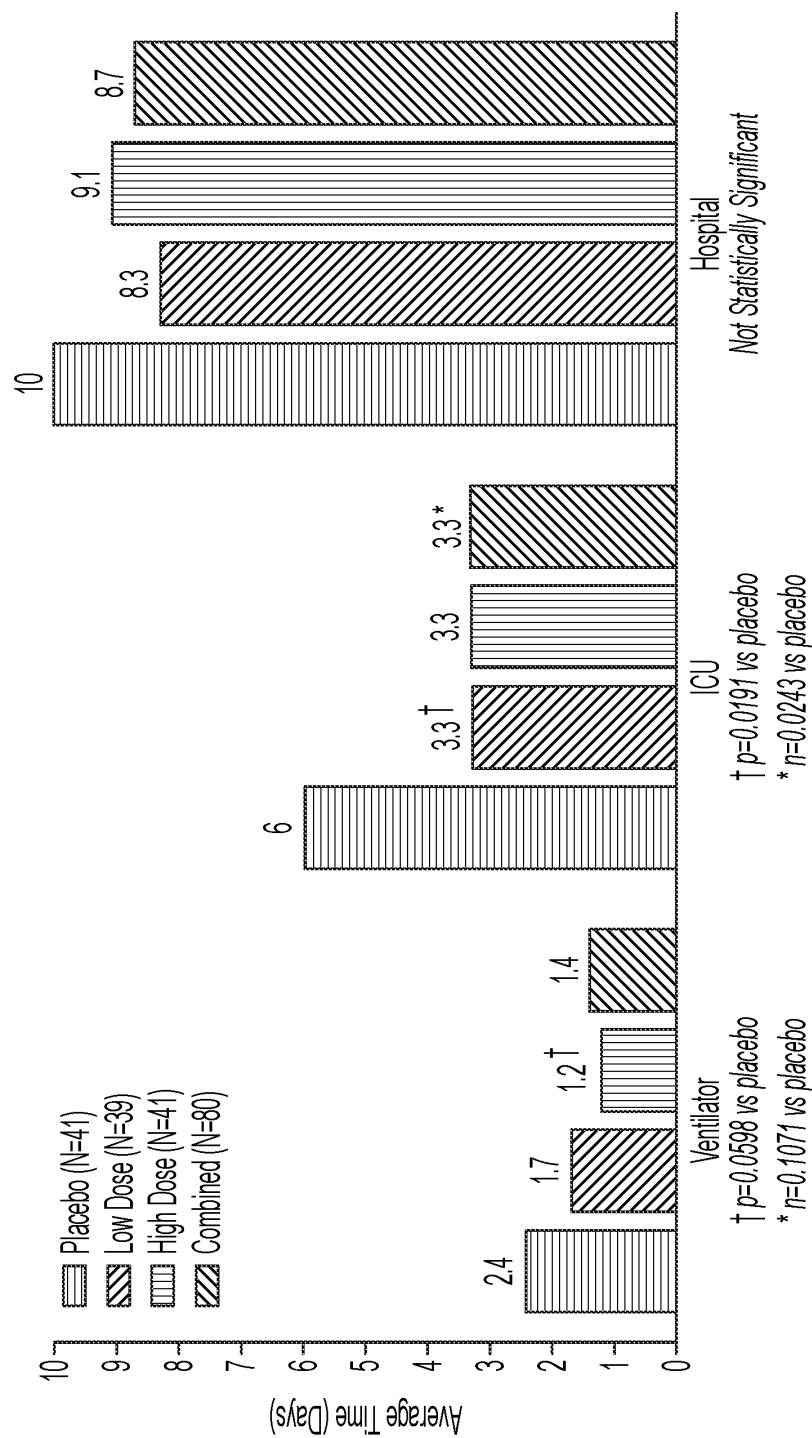


FIG. 4

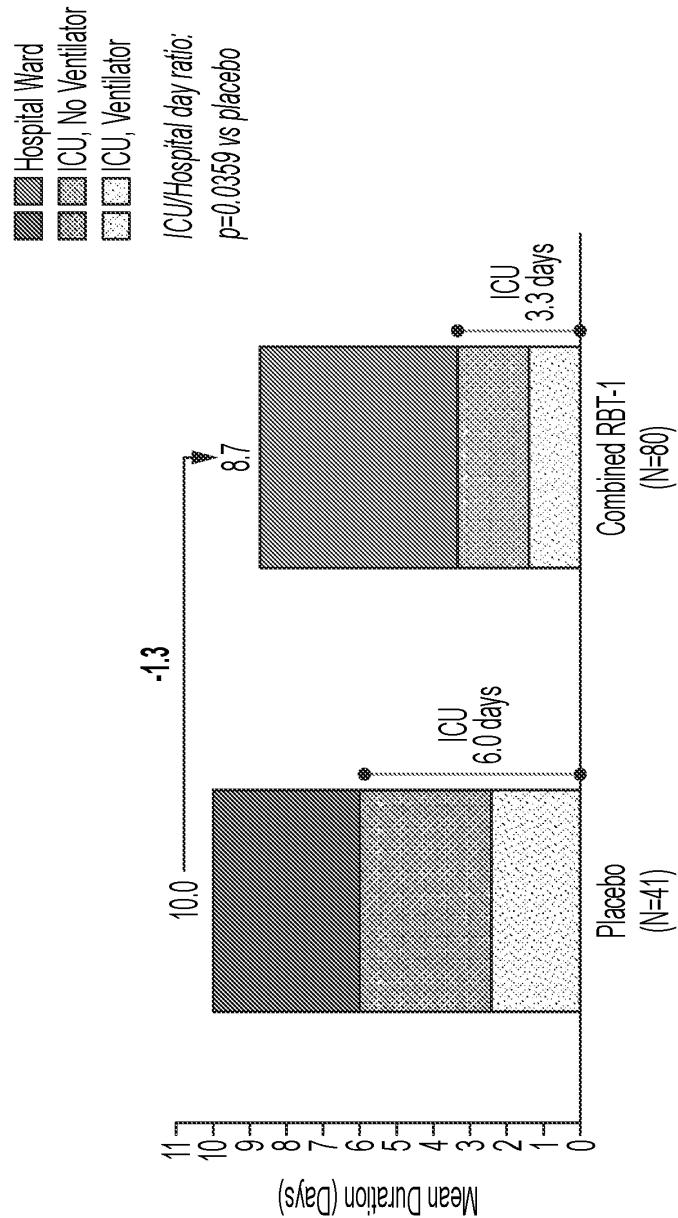


FIG. 5

6/21

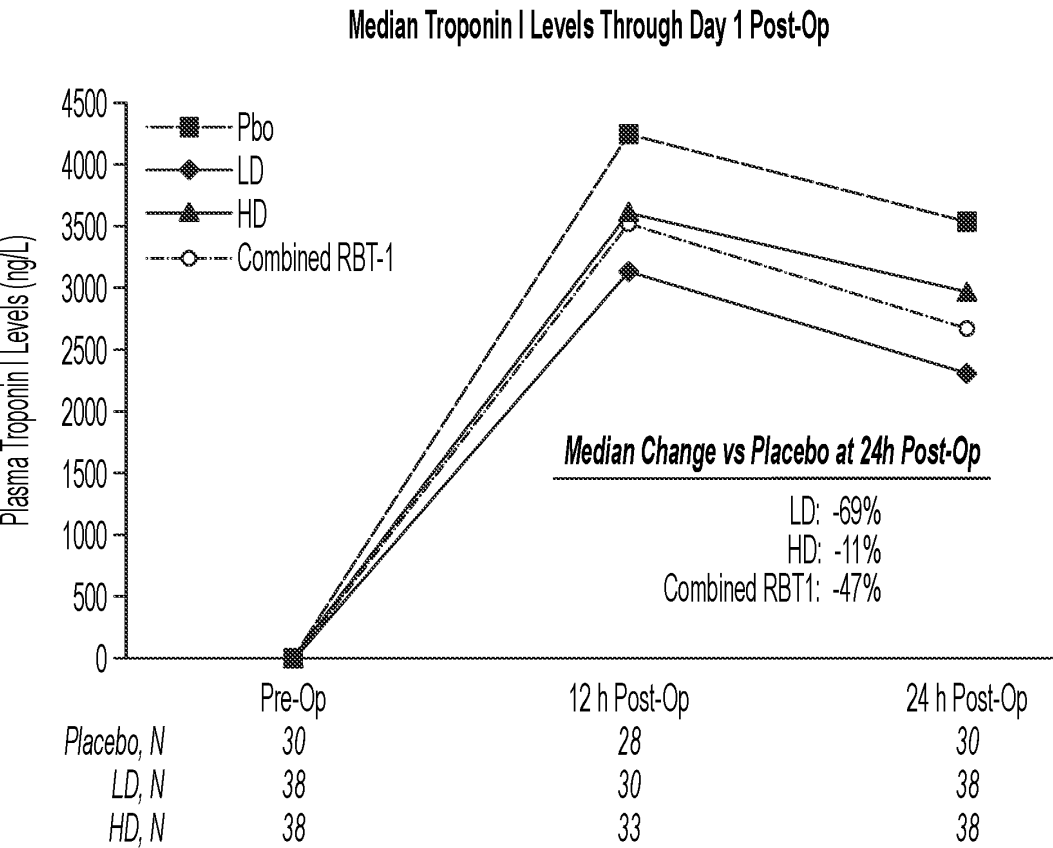


FIG. 6

7/21

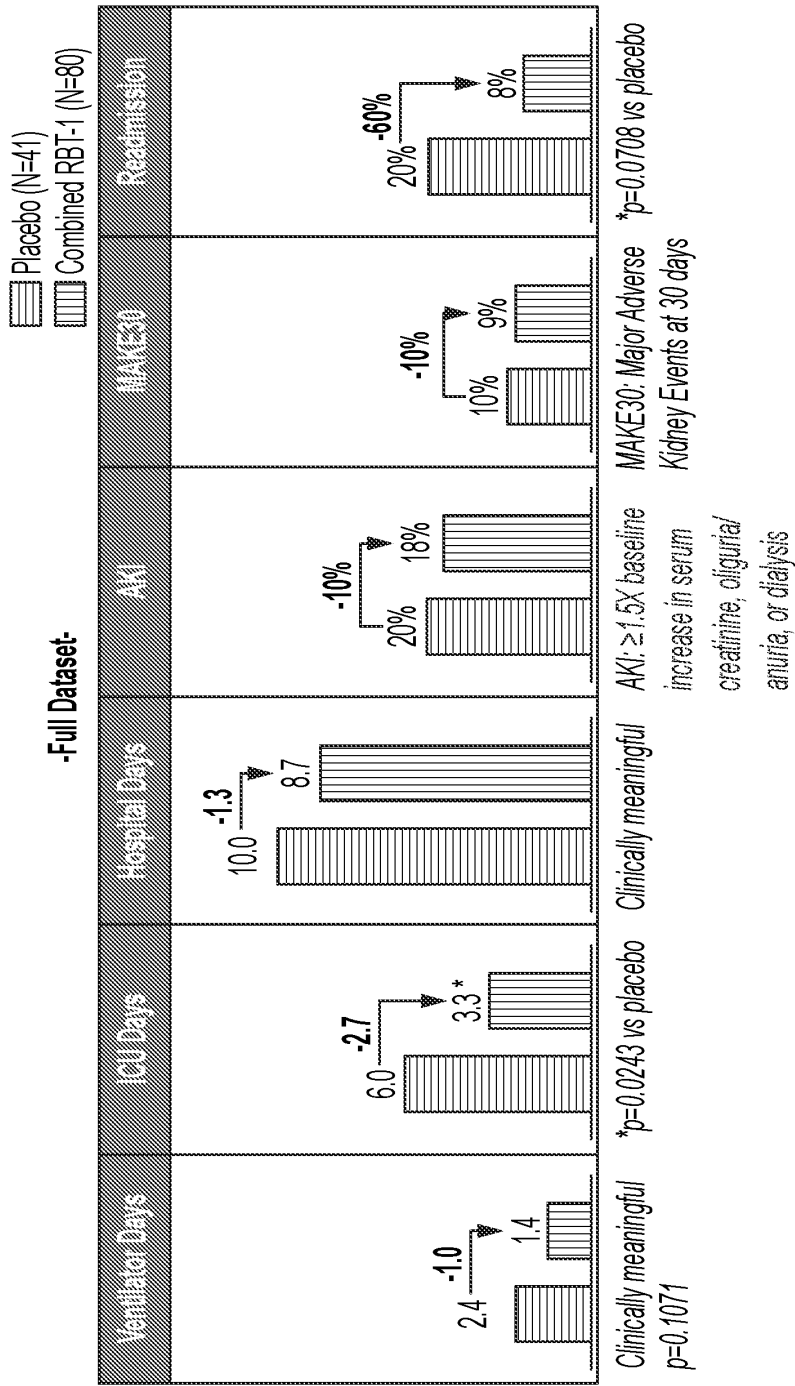


FIG. 7

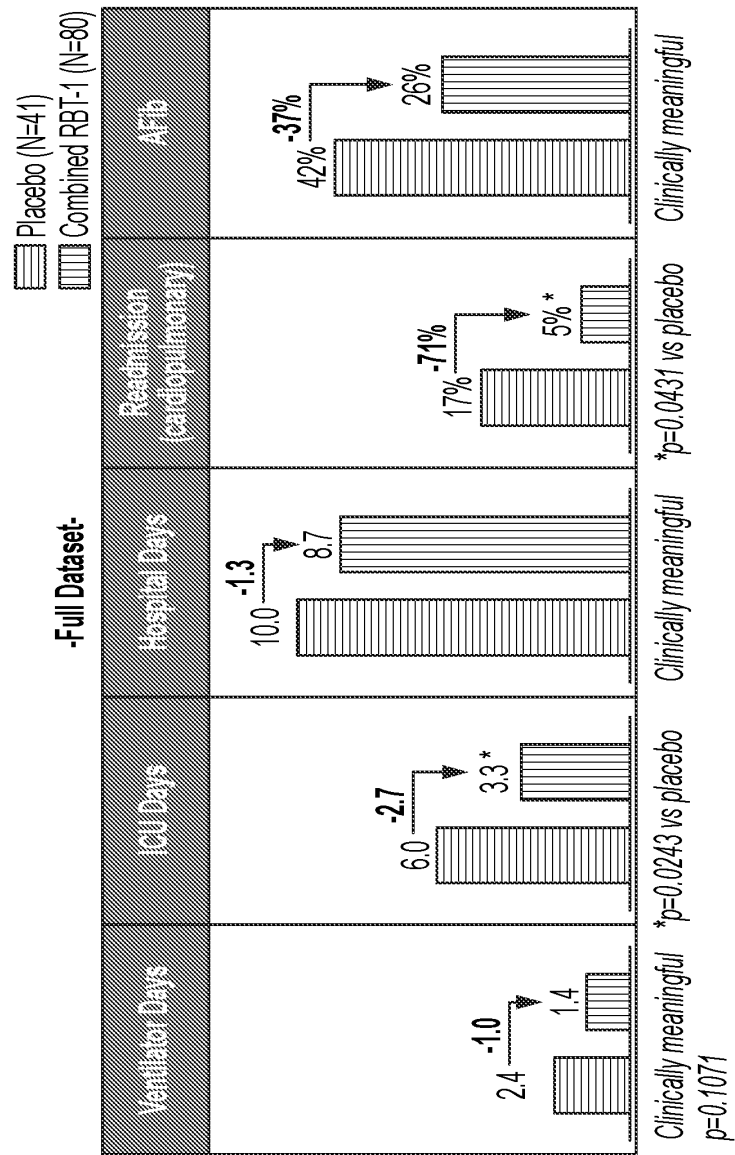


FIG. 8

9/21

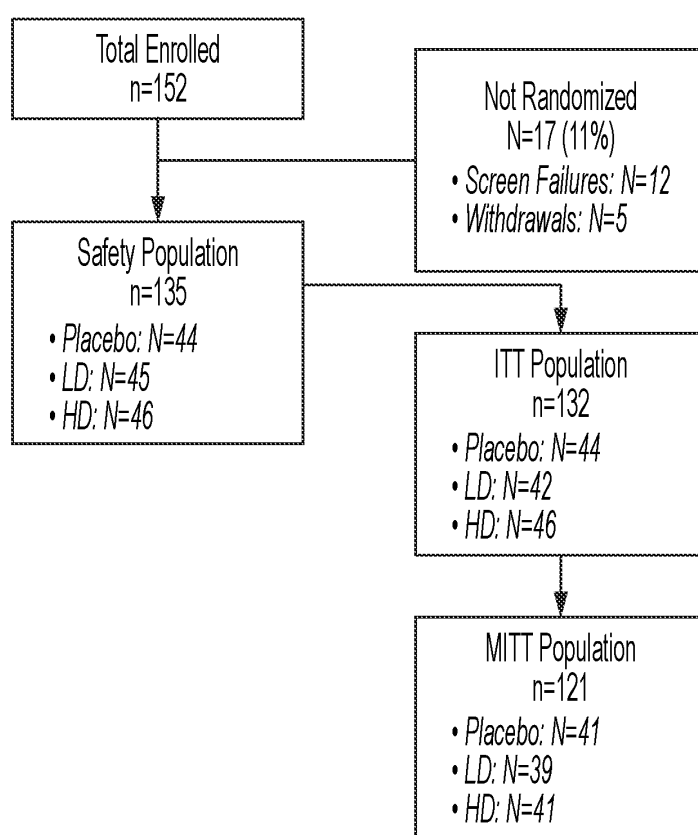


FIG. 9

10/21

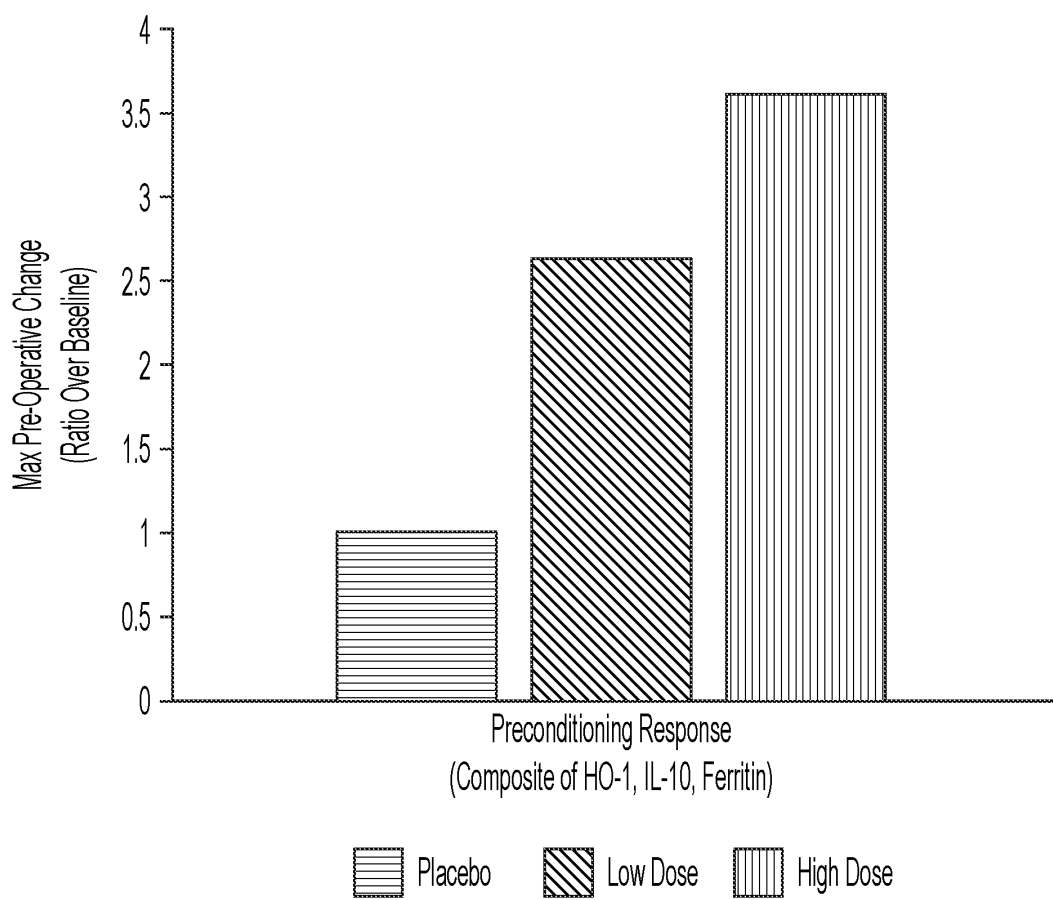


FIG. 10

11/21

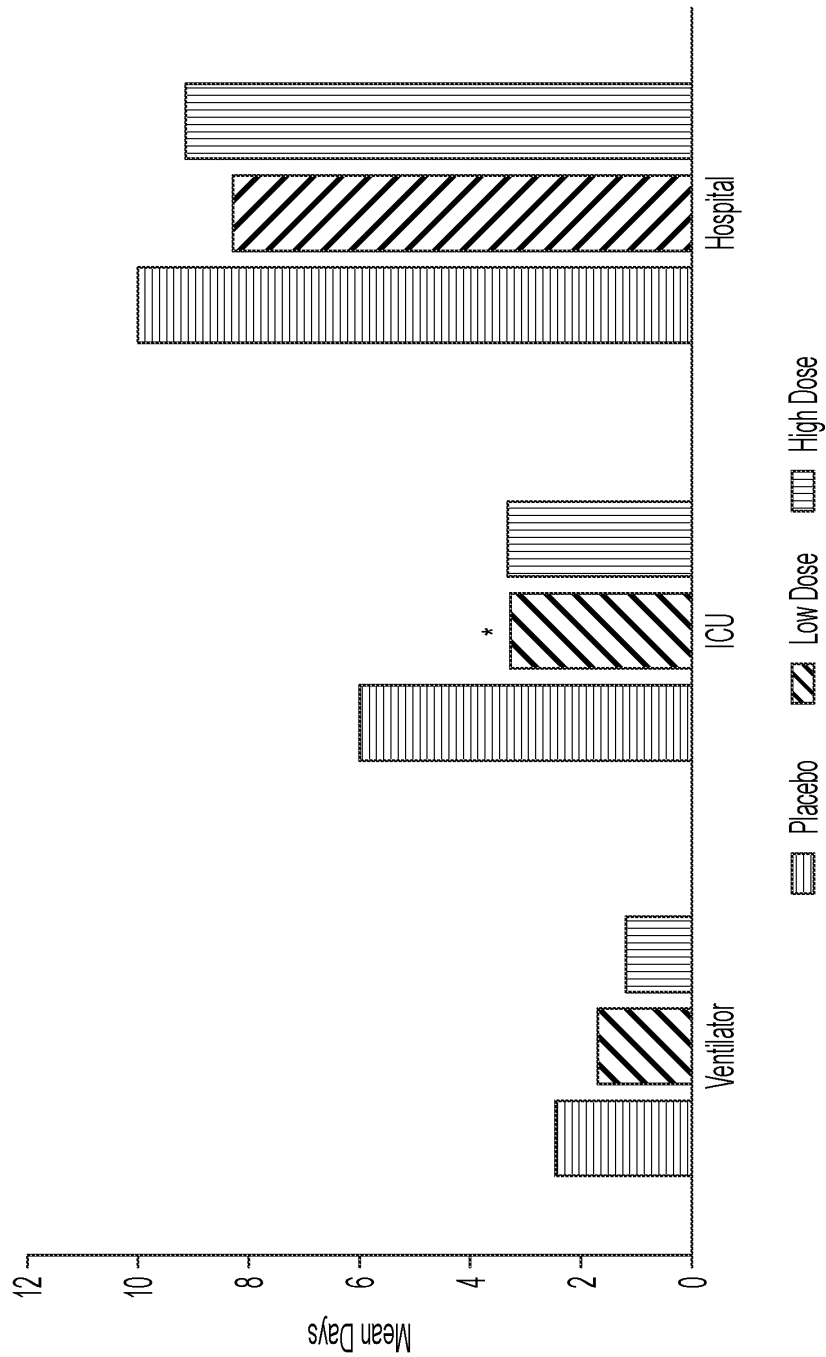


FIG. 11

12/21

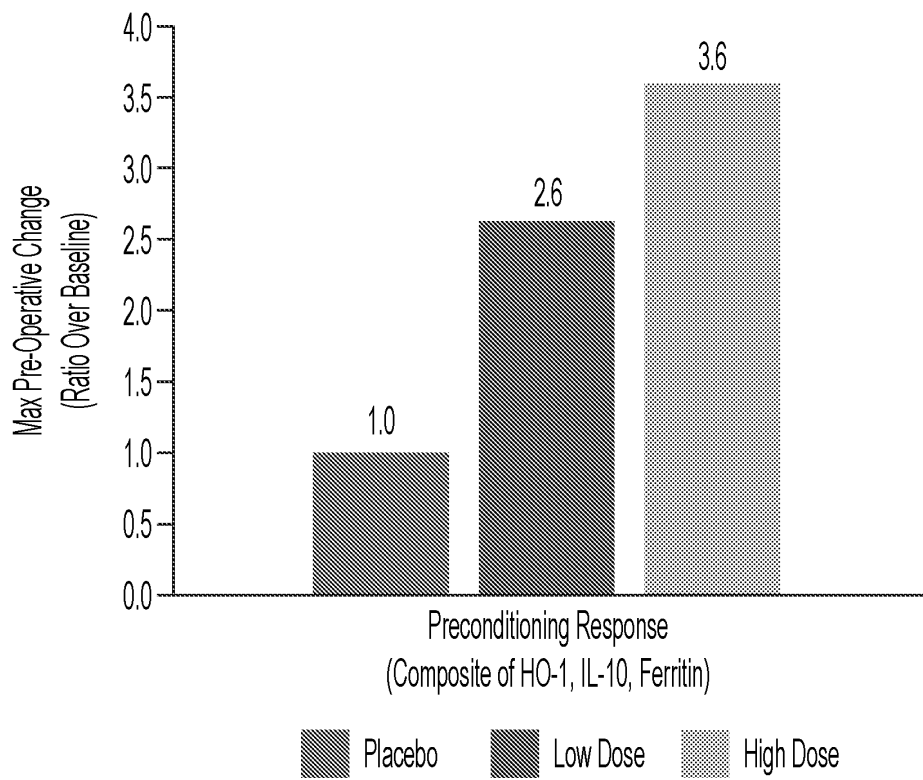


FIG. 12

13/21

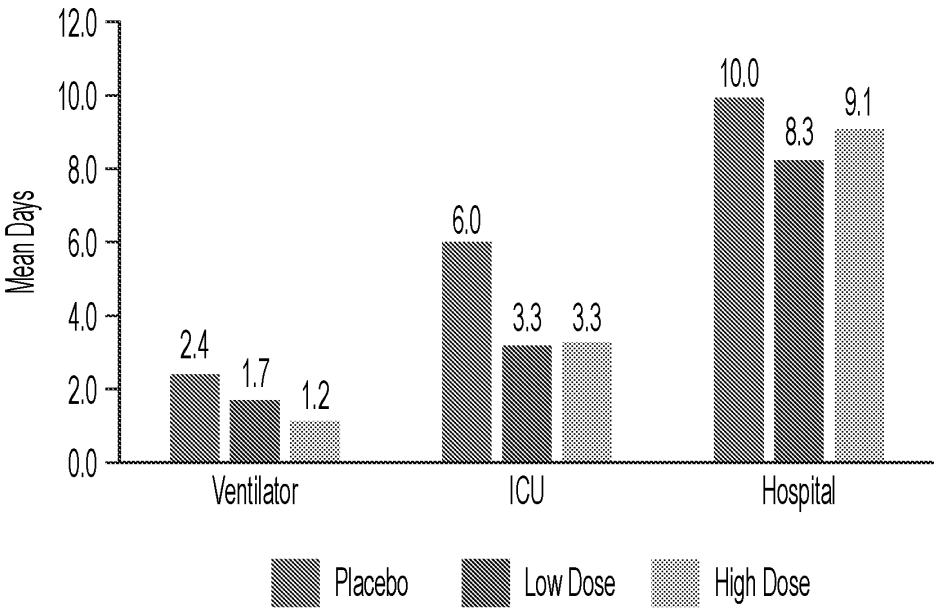


FIG. 13

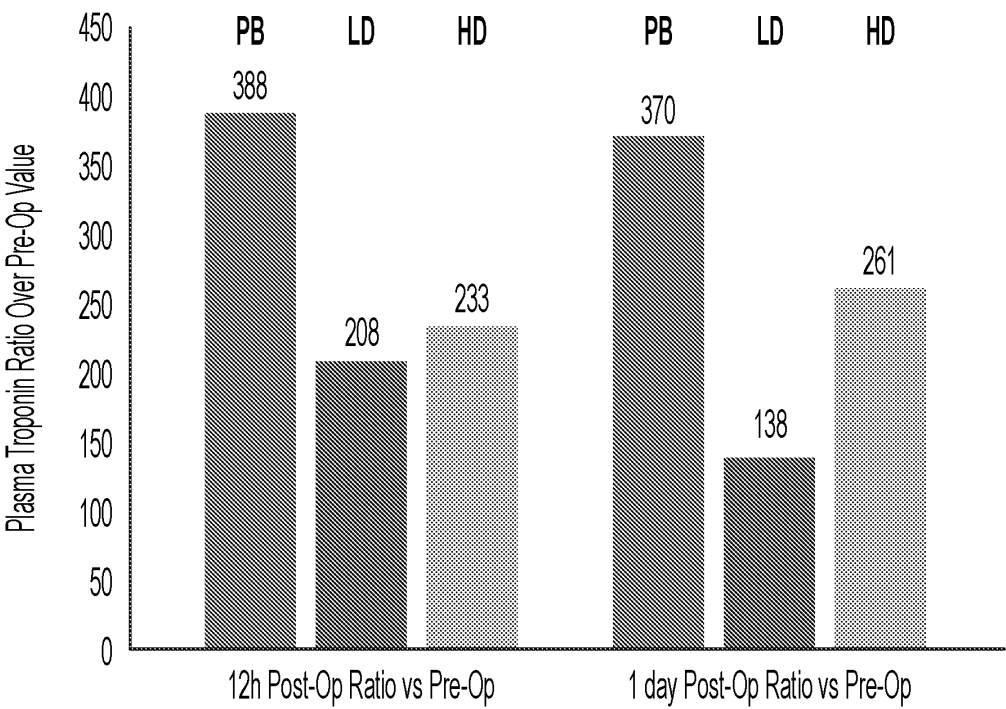


FIG. 14

Table S2: Primary outcome (interim population)

					High-dose vs. placebo		Low-dose vs. placebo	
	High-dose (n=20)	Low-dose (n=19)	Placebo (n=23)		GLSM Ratio (95% CI)	P value	GLSM Ratio (95% CI)	P value
Biomarker response, GLSM*	3.07	2.74	1.03		3.00† (2.30-3.90)	<0.0001	2.67† (2.03-3.53)	<0.0001

Data are GLSM (95% CI) unless otherwise specified. GLSM=geometric least squares mean. *Geometric least squares mean of the ratio of max post-op value over baseline.
†GLSM ratio represents GLSM in the active treatment group over GLSM in the placebo group.

FIG. 15

16/21

Table S3: Baseline characteristics (safety population)

	High-dose (N=46)	Low-dose (N=45)	Placebo (N=44)
Age, mean (min, max), y	66 (37, 86)	64 (46, 82)	66 (19, 81)
Male	36 (78)	34 (76)	32 (73)
Race			
American Indian	1 (2)	0	0
Black	2 (4)	4 (9)	2 (5)
Asian	2 (4)	1 (2)	1 (2)
White	41 (89)	38 (84)	41 (93)
Other	0	2 (4)	0
Weight, mean (min, max), kg	91 (57, 150)	98 (51, 142)	90 (64, 132)
Body mass index, mean (min, max)	30 (20, 49)	32 (18, 48)	30 (19, 45)
EuroSCORE II, mean (min, max)	2.3 (1, 9)	2.6 (1, 17)	2.1 (1, 10)
Low Risk (< 3)	35 (76)	35 (80)	36 (84)
Medium Risk (3 to 6)	9 (20)	4 (9)	5 (12)
High Risk (≥ 6)	2 (4)	5 (11)	2 (5)
Acute kidney injury risk factors			
Age ≥ 65 years	28 (60-9)	25 (55-6)	26 (59-1)
Diabetes mellitus requiring insulin	8 (17-4)	7 (15-6)	4 (9-1)
Congestive heart failure	7 (15-2)	6 (13-3)	7 (15-9)
Heart failure (NYHA III/IV) within 1 year prior to surgery	6 (13-0)	3 (6-7)	3 (6-8)
Previous cardiac surgery with sternotomy	1 (2-2)	2 (4-4)	0
Left ventricular ejection fraction ≤ 35%	5 (10-9)	6 (13-3)	2 (4-5)
Estimated glomerular filtration rate ≥ 20 to < 60 mL/min/1.73m ²	13 (28-3)	13 (28-9)	8 (18-2)
Pre-operative anemia (hemoglobin < 10 g/dL)	0	1 (2-2)	1 (2-3)
Hospitalized for management of cardiac or pulmonary disease	11 (23-9)	6 (13-3)	8 (18-2)
Time from infusion to surgery, mean (SD), h	94 ± 197-4	84 ± 169-9	45 ± 35-3
Time on cardiopulmonary bypass, mean (SD), h	2-0 ± 1-2	1-9 ± 0-8	1-9 ± 1-0
Surgery Type			
CABG alone	24 (52)	24 (53)	22 (50)
Valve alone	11 (24)	15 (33)	8 (18)
CABG + Valve	11 (24)	6 (13)	14 (32)

Data are n (%) unless otherwise specified. CABG=coronary artery bypass grafting. EuroSCORE=European system for cardiac operative risk evaluation. NYHA=New York Heart Association.

FIG. 16**SUBSTITUTE SHEET (RULE 26)**

17/21

Table S4: Baseline characteristics (modified intent-to-treat population)

	High-dose (n=41)	Low-dose (n=39)	Placebo (n=41)
Age, mean $\pm$ SD, y	67 $\pm$ 11-1	65 $\pm$ 8-2	65 $\pm$ 11-0
Male	32 (78)	28 (72)	30 (73)
Race			
American Indian	1 (2)	0	0
Black	1 (2)	4 (10)	2 (5)
Asian	2 (5)	1 (3)	1 (2)
White	37 (90)	32 (82)	38 (93)
Other	0	2 (5)	0
Weight, mean $\pm$ SD, kg	91 $\pm$ 20-2	98 $\pm$ 20-8	89 $\pm$ 18-5
Body mass index, mean $\pm$ SD	30 $\pm$ 6-7	33 $\pm$ 6-3	30 $\pm$ 5-5
EuroSCORE II, mean $\pm$ SD	2.4 $\pm$ 1-9	2.8 $\pm$ 3-9	2.1 $\pm$ 1-9
Low Risk (< 3)	31 (76)	31 (80)	35 (85)
Medium Risk (3 to 6)	8 (20)	3 (8)	4 (10)
High Risk ($\geq$ 6)	2 (5)	5 (13)	2 (5)
Acute kidney injury risk factors			
Age $\geq$ 65 years	25 (61-0)	23 (59-0)	23 (56-1)
Diabetes mellitus requiring insulin	8 (19-5)	6 (15-4)	3 (7-3)
Congestive heart failure	7 (17-1)	5 (12-8)	6 (14-6)
Heart failure (NYHA III/IV) within 1 year prior to surgery	5 (12-2)	3 (7-7)	2 (4-9)
Previous cardiac surgery with sternotomy	1 (2-4)	1 (2-6)	0
Left ventricular ejection fraction $\leq$ 35%	4 (9-8)	5 (12-8)	2 (4-9)
Estimated glomerular filtration rate $\geq$ 20 to < 60 mL/min/1.73m ²	13 (31-7)	13 (33-3)	6 (14-6)
Pre-operative anemia (hemoglobin < 10 g/dL)	0	1 (2-6)	1 (2-4)
Hospitalized for management of cardiac or pulmonary disease	11 (26-8)	5 (12-8)	8 (19-5)
Time from infusion to surgery, mean $\pm$ SD, h	38 $\pm$ 9-4	39 $\pm$ 9-2	39 $\pm$ 9-9
Time on cardiopulmonary bypass, mean $\pm$ SD, h	2-0 $\pm$ 1-2	2-0 $\pm$ 0-8	2-0 $\pm$ 1-0
Surgery Type			
CABG alone	24 (59)	20 (51)	20 (49)
Valve alone	9 (22)	13 (33)	7 (17)
CABG + Valve	8 (20)	6 (15)	14 (34)

Data are n (%) unless otherwise specified. CABG=coronary artery bypass grafting. EuroSCORE=European system for cardiac operative risk evaluation. NYHA=New York Heart Association.

FIG. 17**SUBSTITUTE SHEET (RULE 26)**

18/21

Table S5: Other prespecified outcomes (modified intent-to-treat population)

	High-dose (n=41)	Low-dose (n=39)	Placebo (n=41)	High-dose vs. Placebo, risk difference (95% CI)	Low-dose vs. Placebo, risk difference (95% CI)
Death	2 (5%)	1 (3%)	3 (7%)	-2.4 (-15.6 to 10.6)	-4.8 (-18.1 to 7.1)
Acute kidney injury requiring dialysis	1 (2%)	0 (0%)	1 (2%)	0.0 (-10.6 to 10.6)	-2.4 (-13.2 to 7.0)
MAKE30	4 (10%)	1 (3%)	4 (10%)	0.0 (-)	-7.2 (-)
MAKE60	3 (7%)	1 (3%)	2 (5%)	2.3 (-)	-2.4 (-)
MAKE90	3 (7%)	1 (3%)	2 (5%)	2.3 (-)	-2.4 (-)
Atrial fibrillation	10 (24%)	12 (31%)	17 (42%)	-17.1 (-36.8 to 3.6)	-10.7 (-31.6 to 10.7)
Hypervolemia	4 (10%)	3 (8%)	10 (24%)	-14.6 (-32.1 to 2.1)	-16.7 (-33.7 to 0.0)
Days on ventilator	1.2 ± 0.7	1.7 ± 2.7	2.4 ± 4.3	-1.3 (-2.6 to 0.0)	-0.7* (-2.0 to 0.6)
Days in ICU	3.3 ± 2.3	3.3 ± 3.6	6.0 ± 9.0	-2.7 (-5.2 to -0.2)	-2.7* (-5.3 to -0.2)
Days in hospital	9.1 ± 8.2	8.3 ± 3.9	10.0 ± 9.2	-0.9 (-4.2 to 2.4)	-1.7* (-5.0 to 1.6)
30-day readmission†					
All	4 (10%)	2 (5%)	8 (21%)	-10.8 (-28.5 to 6.8)	-15.8 (-33.3 to 0.0)
Cardiopulmonary‡	2 (5%)	2 (5%)	7 (18%)	-13.3 (-29.5 to 1.5)	-13.2 (-29.6 to 2.2)
60-day readmission†					
All	5 (13%)	3 (8%)	10 (26%)	-13.5 (-31.9 to 4.8)	-18.4 (-35.9 to -1.2)
Cardiopulmonary‡	2 (5%)	2 (5%)	8 (21%)	-15.9 (-32.6 to -0.6)	-15.8 (-33.3 to 0.0)

Data are n (%) or mean ± SD unless otherwise specified. Percentages are rounded. ICU=intensive care unit. MAKE=major adverse kidney event. *Absolute mean difference. †Subjects who died during index hospitalization were excluded from readmission analysis; total sample size for high-dose, low-dose, and placebo groups were 39, 38, and 38 patients, respectively. ‡Readmissions for cardiopulmonary and all causes were identical at 60 days and 90 days.

FIG. 18

Table S6: Hierarchical composite outcome (win ratio)

	Wins	Ties	Losses	Win Ratio (95% CI)*
High-dose RBT-1 vs. placebo	891	142	648	1.39 (0.80-2.42)
Low-dose RBT-1 vs. placebo	985	178	436	2.26 (1.23-4.15)

Data are number of wins, ties, or losses for each RBT-1 vs. placebo pair in the modified intent-to-treat population. *The win ratio, based on the Finkelstein-Schoenfeld method, was the hierarchical composite of death > acute kidney injury requiring dialysis > ICU days > 30-day cardiopulmonary readmission in each patient in the high-dose and low-dose RBT-1 groups compared with each patient in the placebo group (> denotes the order of the win ratio hierarchy, which decreases from left to right).

FIG. 19

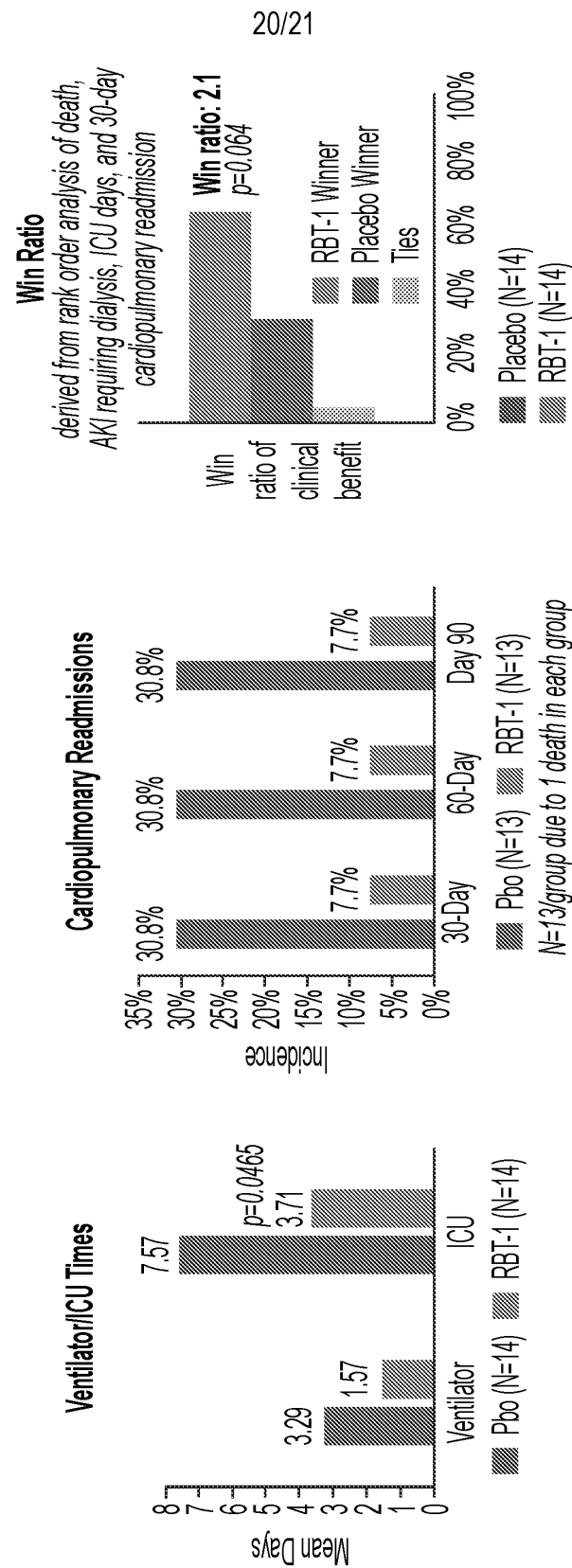


FIG. 20

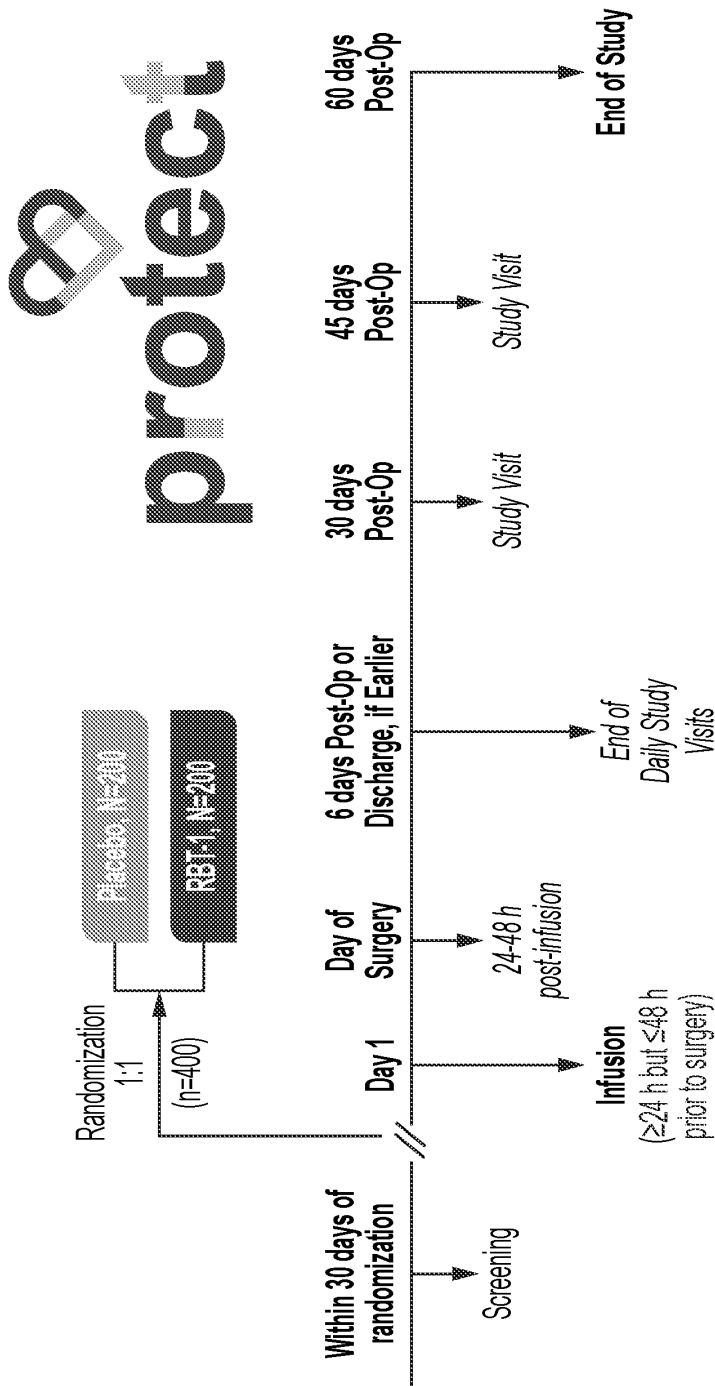


FIG. 21