Results of a Phase 2 Study With RBT-1 Evaluating Postoperative Course in Patients Undergoing Elective CABG/Valve Surgery on Cardiopulmonary Bypass

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On behalf of START investigators

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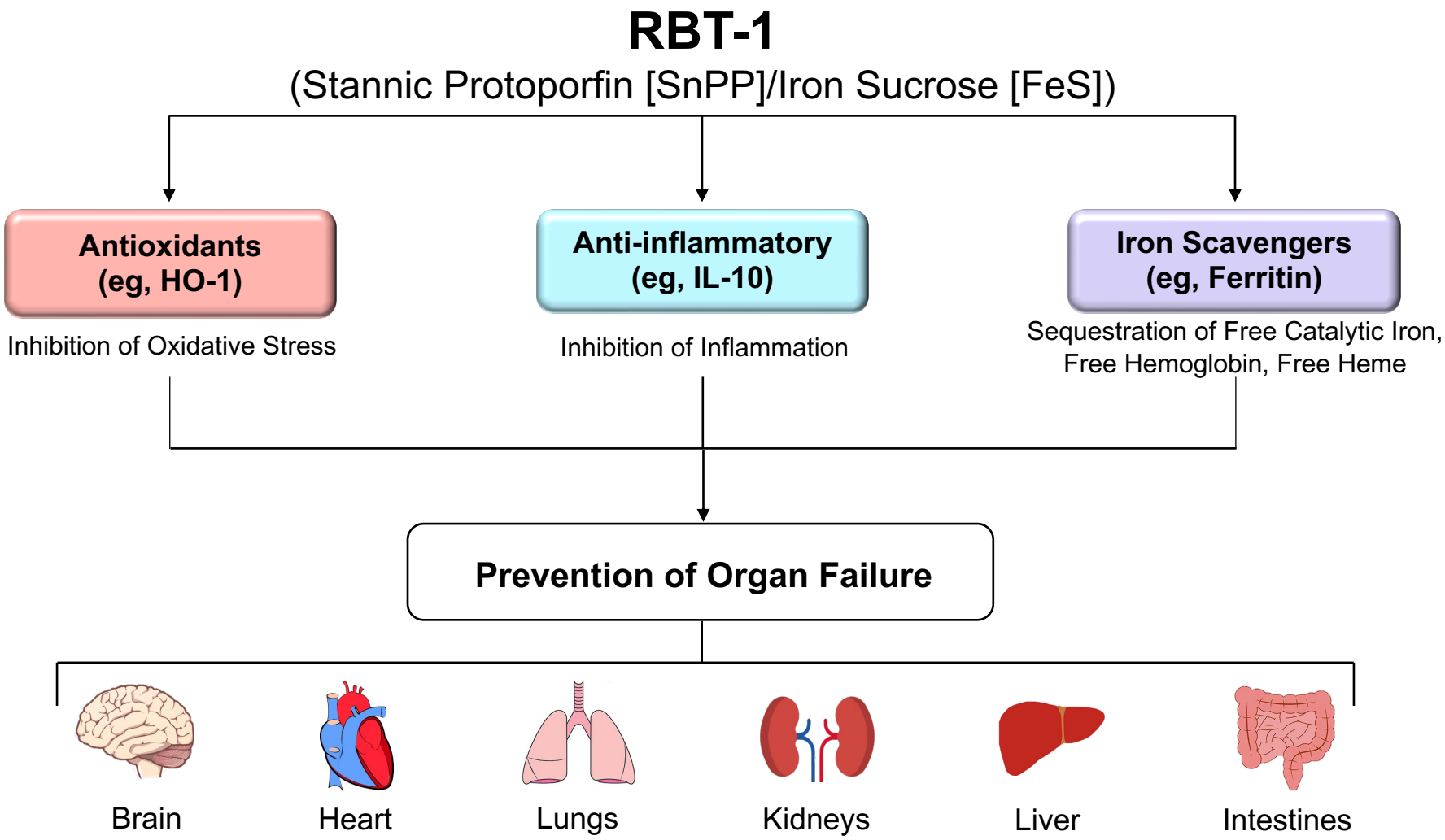
Topline Data

Preconditioning as a means for organ protection

- **Preconditioning** involves **priming a stress response** to **elicit protection against subsequent injury**
- **As early as 1929**, it was observed that the **kidneys of animals** previously exposed to (**preconditioned** by) various minor stressors **acquired resistance to organ failure**
- **In the early 1990s, remote ischemic preconditioning (RIPC)**, which involves a brief induction of ischemia and reperfusion to distal tissues using a sphygmomanometer in the upper arm or leg, was introduced
- **RIPC** has been attempted in several clinical studies to recapitulate the preconditioning effect observed in animals – **large trials have been negative, likely due to inconsistent effect of remote ischemia on target organ, and an inability to determine the dose of ischemia**

RBT-1 – Pharmacologic Approach to Preconditioning

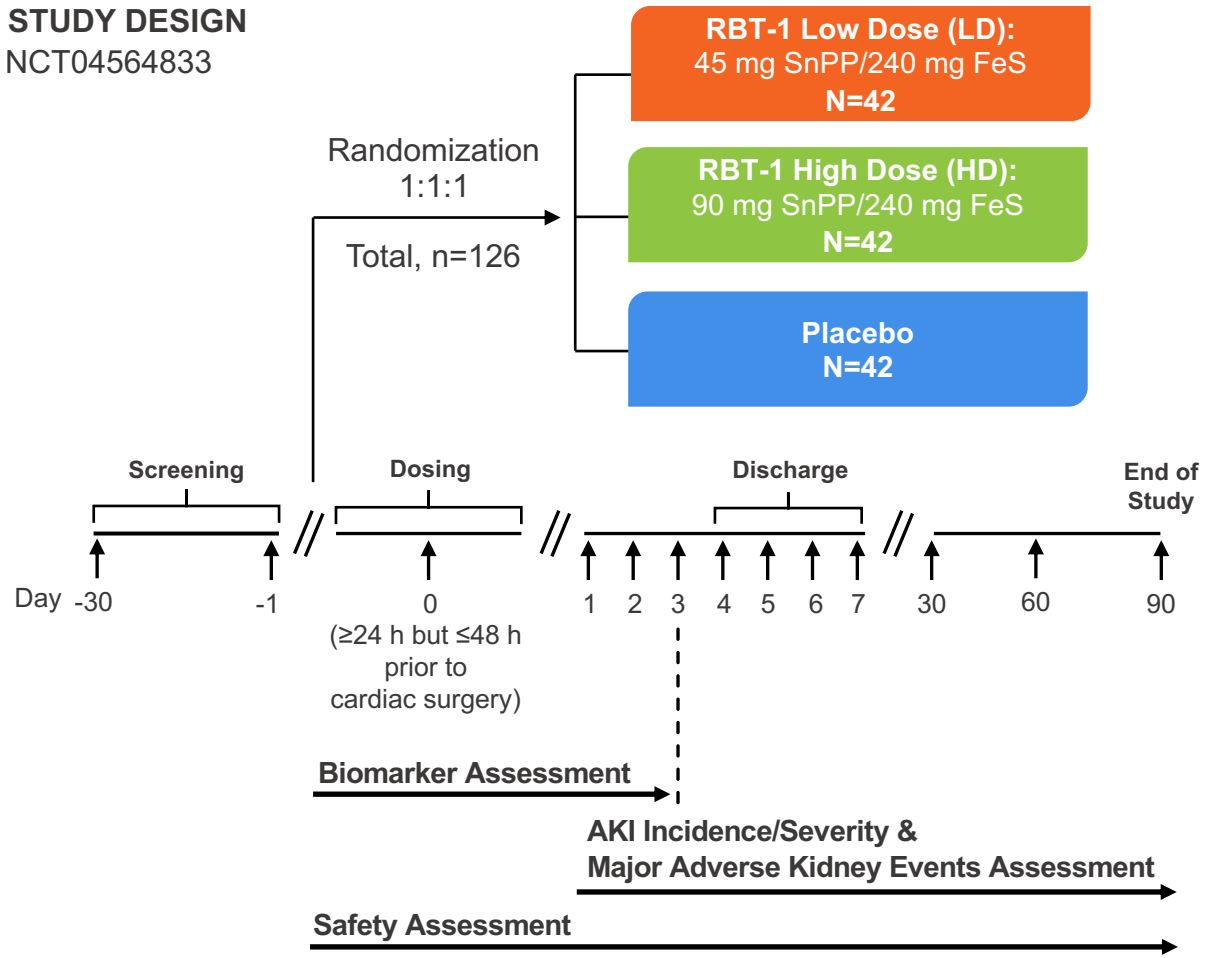
The **mechanism of action of RBT-1** is applicable to **multiorgan protection**



Phase 2 Study of RBT-1 in Subjects Undergoing CABG and/or Valve Surgery on Cardiopulmonary Bypass

Randomized, double-blind, placebo-controlled, multi-center (US, Canada, Australia)

STUDY DESIGN
NCT04564833



Primary Objective

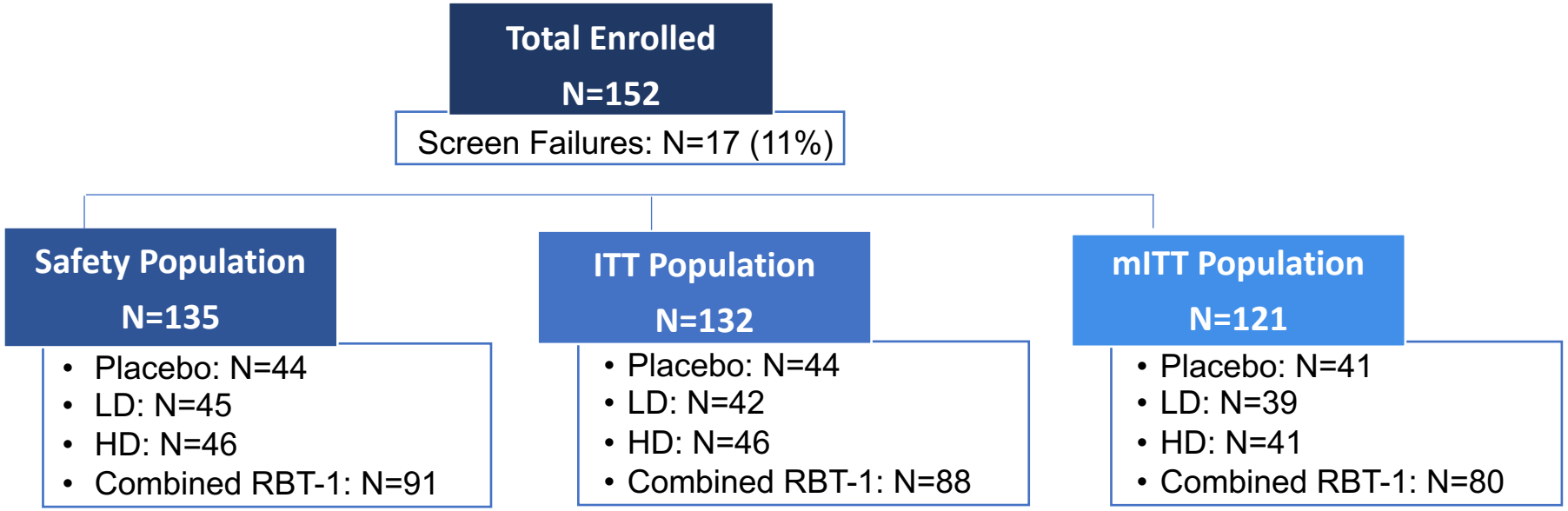
Effect of RBT-1 in generating a **preconditioning response**, measured by a **composite of plasma biomarkers** (heme oxygenase-1 [**HO-1**], **ferritin**, and interleukin-10 [**IL-10**]) from Baseline (pre-dose) through Day 1 pre-surgery.

Key Secondary and Exploratory Objectives

- Days on **ventilator**
- Days in intensive care unit (**ICU**)
- **Hospital length of stay**
- Incidence of acute kidney injury (**AKI**)
- Incidence of Major Adverse Kidney Events (**MAKE**)
- Hospital **readmission rate**
- Safety

RBT-1 Phase 2 Patient Population

- The overall study population was **not enriched** for events
- Subjects were **randomized at site level** to account for differences in standard of care



- **Safety population:** All subjects who received any amount of study drug
- **ITT population:** All subjects who *received study drug* and *had biomarker assessments performed at Baseline and prior to surgery*
- **mITT population:** All subjects who *received study drug*, underwent cardiac *surgery without delay*, and were *evaluated through the end of index surgery hospitalization*

Demographics

mITT Population

	Placebo (N=41)	Combined RBT-1 (N=80)	Low Dose (N=39)	High Dose (N=41)
Mean Age (yrs)	65.37	65.61	64.59	66.59
Sex				
Female, N (%)	11 (26.8)	20 (25.0)	11(28.2)	9 (22.0)
Male, N (%)	30 (73.2)	60 (75.0)	28 (71.8)	32 (78.0)
Race				
American Indian	0	1 (1.3)	0	1 (2.4)
Black, N (%)	2 (4.9)	5 (6.3)	4 (10.3)	1 (2.4)
Asian, N (%)	1 (2.4)	3 (3.8)	1 (2.6)	2 (4.9)
White, N (%)	38 (92.7)	69 (86.3)	32 (82.1)	37 (90.2)
Other, N (%)	0	2 (2.5)	2 (5.1)	0
Weight (kg), Mean (min, max)	88.7 (64, 132)	94.0 (51, 150)	97.4 (51, 142)	90.9 (57, 150)
BMI (kg/m^2), Mean (min, max)	29.7 (19, 45)	31.4 (18, 49)	32.8 (18, 48)	30.2 (20, 49)

Baseline Risk Factors: EuroSCORE II

mITT Population

EuroSCORE	Placebo (N=41)	Combined RBT-1 (N=80)	Low Dose (N=39)	High Dose (N=41)
Mean	1.89	2.57	2.76	2.39
Median	1.47	1.55	1.06	1.93
Low Risk (< 3), N (%)	36 (87.8)	60 (76.3)	31 (79.5)	30 (73.2)
Medium Risk (3 to 6), N (%)	3 (7.3)	12 (15.0)	3 (7.7)	9 (22.0)
High Risk (≥ 6), N (%)	2 (4.9)	7 (8.8)	5 (12.8)	2 (4.9)

Investigational Drug and Surgery Characteristics

mITT Population

	Placebo (N=41)	Combined RBT-1 (N=80)	Low Dose (N=39)	High Dose (N=41)
Time of Infusion Before Surgery Mean (hrs)	38.6	38.5	38.6	38.4
Surgery Type				
CABG Alone, N (%)	20 (48.8)	44 (55.0)	20 (51.3)	24 (58.5)
Valve Alone, N (%)	7 (17.1)	22 (27.5)	13 (33.3)	9 (22.0)
CABG + Valve, N (%)	14 (34.1)	14 (17.5)	6 (15.4)	8 (19.5)
Duration of Surgery Mean (hrs)	4.9	4.9	5.0	4.9
Time on Pump Mean (hrs)	1.94	1.97	1.95	1.99

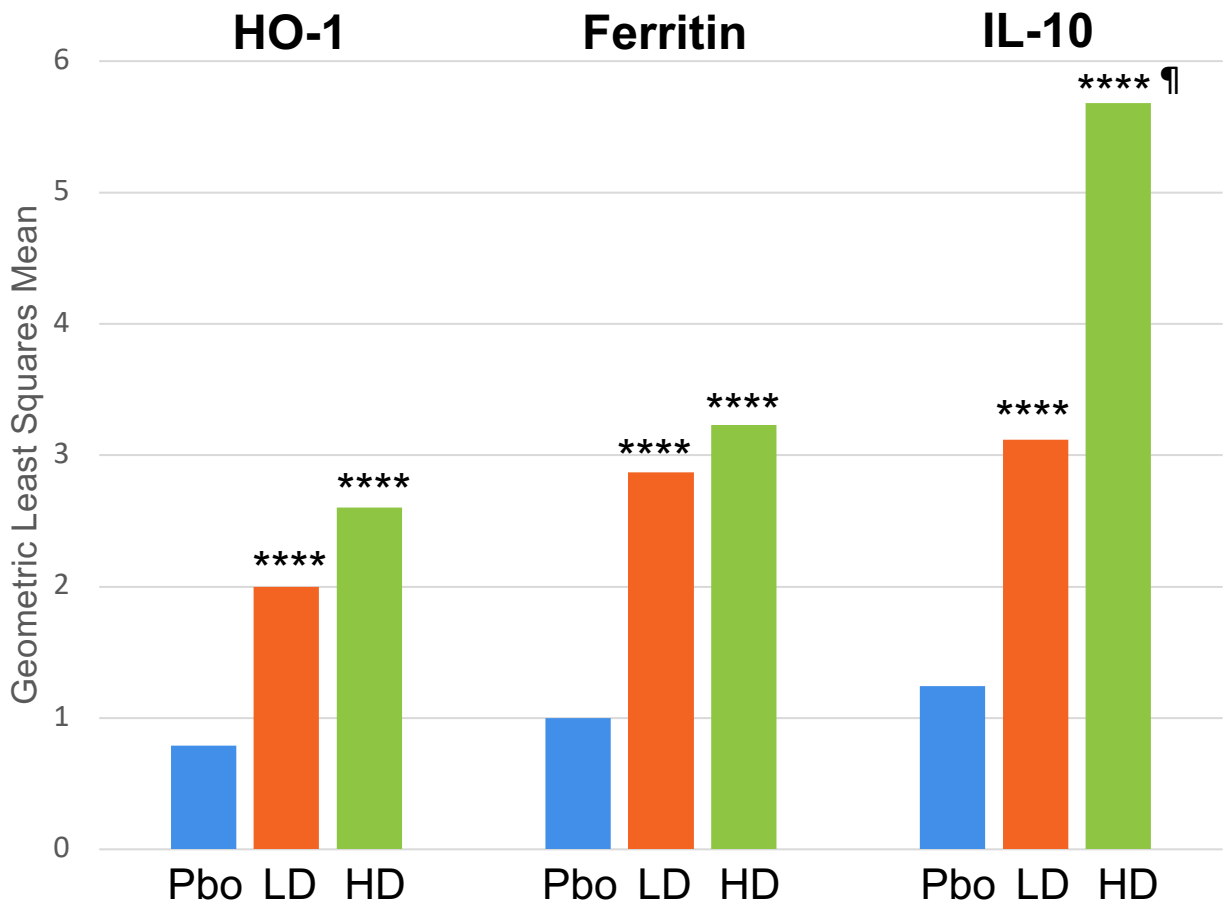
Statistically Significant Increase in Cytoprotective Response Biomarkers with Both Doses of RBT-1

mITT Population

Primary Endpoint Met

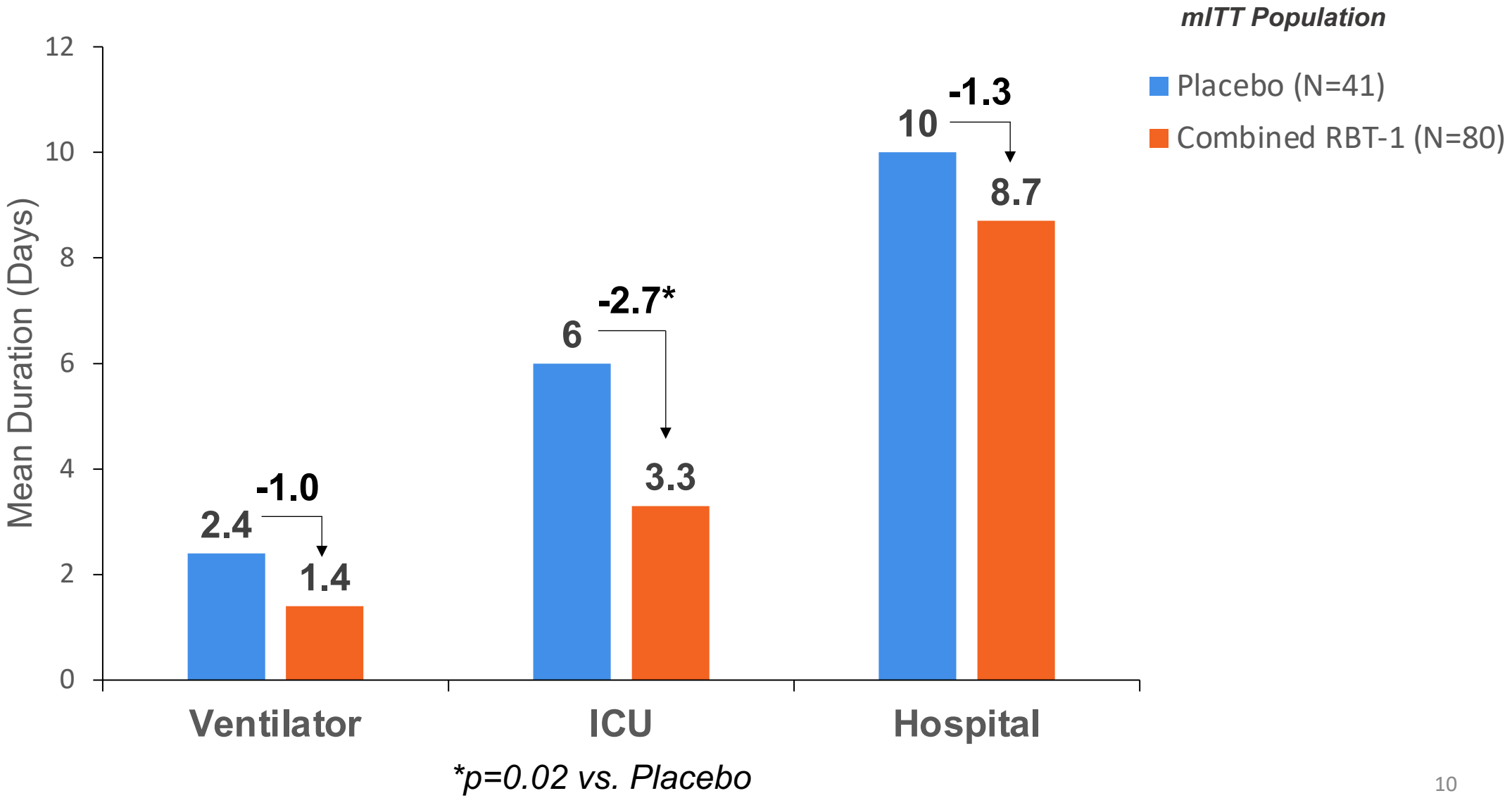
Composite Biomarker Response

	Placebo (N=41)	Low Dose (N=39)	High Dose (N=41)
Mean	0.98	2.65	3.62
P-value vs Pbo		<0.0001	<0.0001
P-value LD vs HD			0.0046



*****p<0.0001 vs. Pbo* ¶ *p=0.0025, HD vs LD*

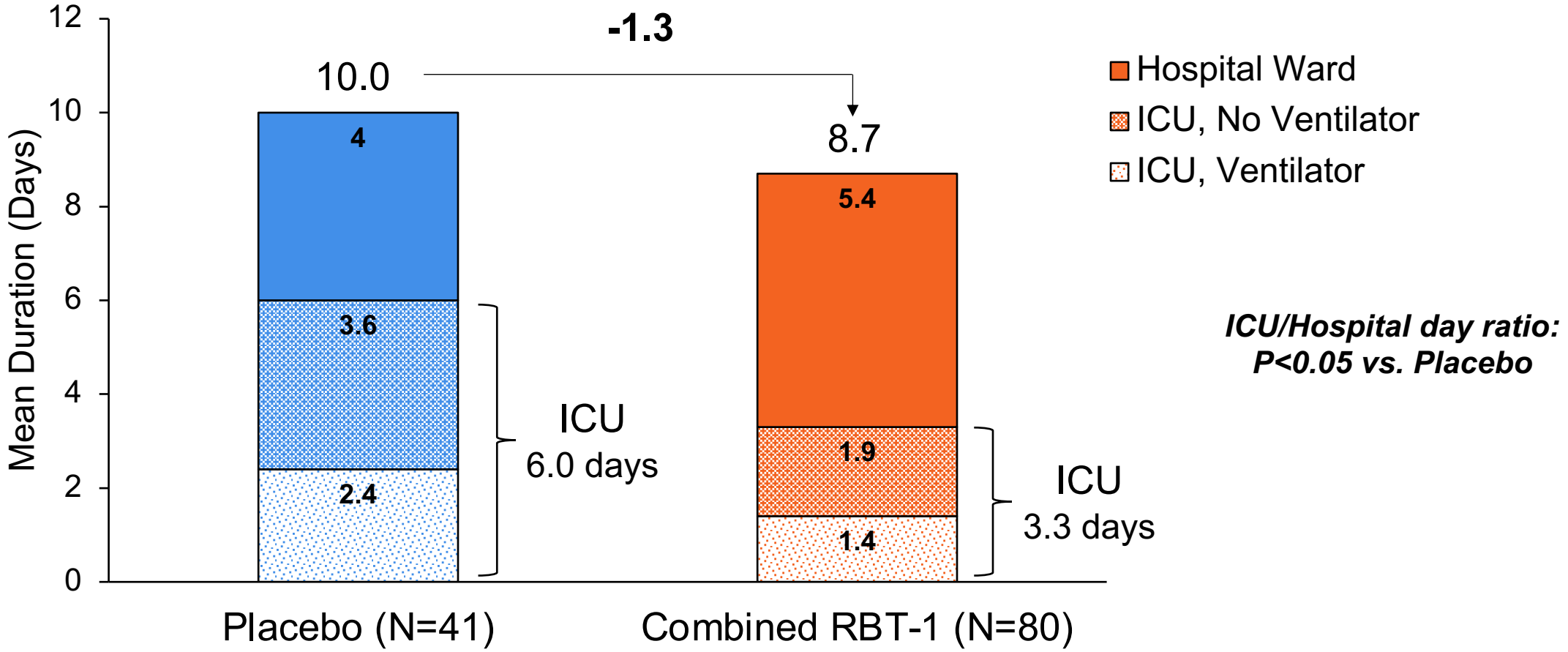
Statistically Significant Reduction in ICU Time in Patients Treated with RBT-1



*p=0.02 vs. Placebo

Improvement in Mean Composition of Hospitalization in Patients Treated with RBT-1

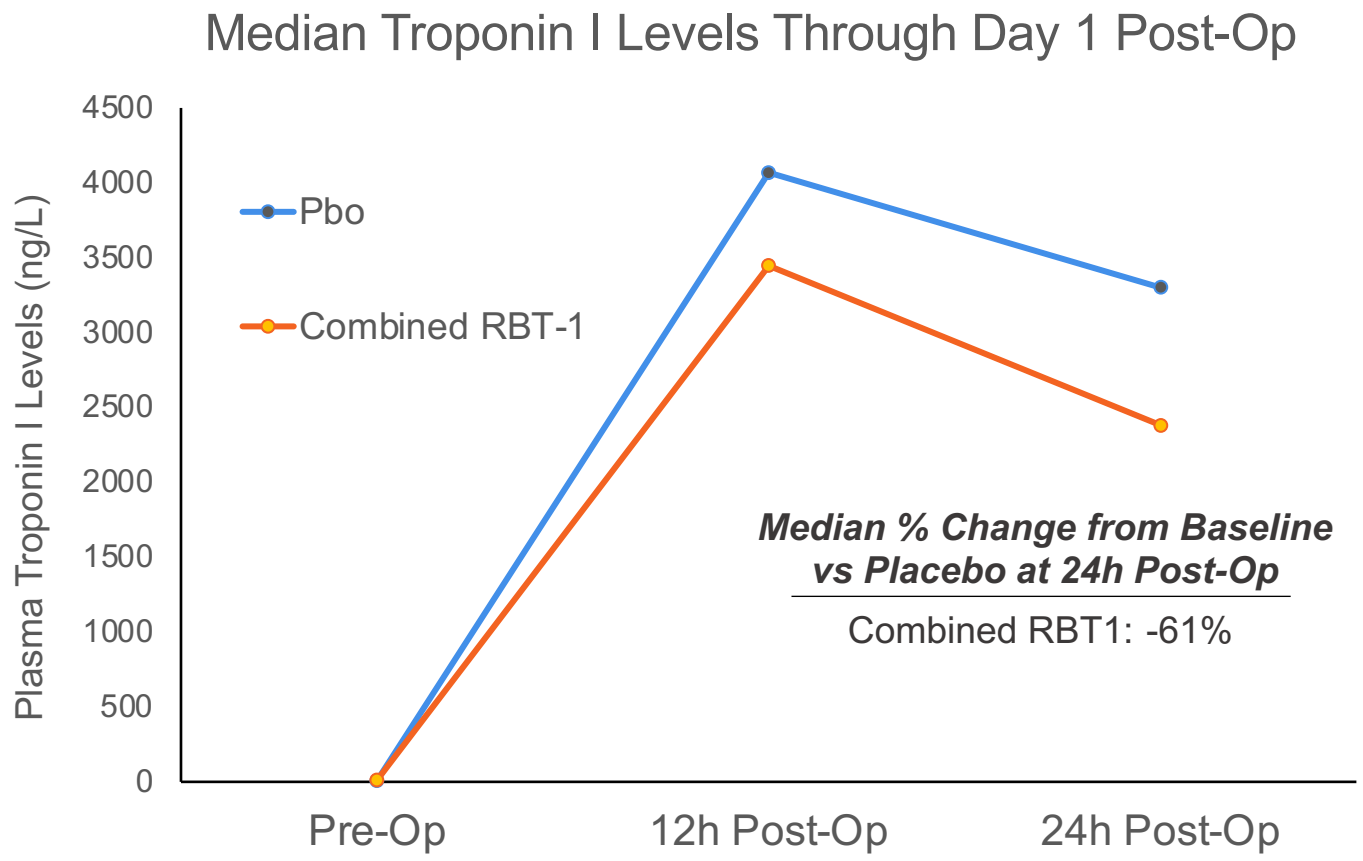
mITT Population



ICU/Hospital day ratio: P<0.05 vs. Placebo

Changes in Troponin I in Patients Treated with RBT-1

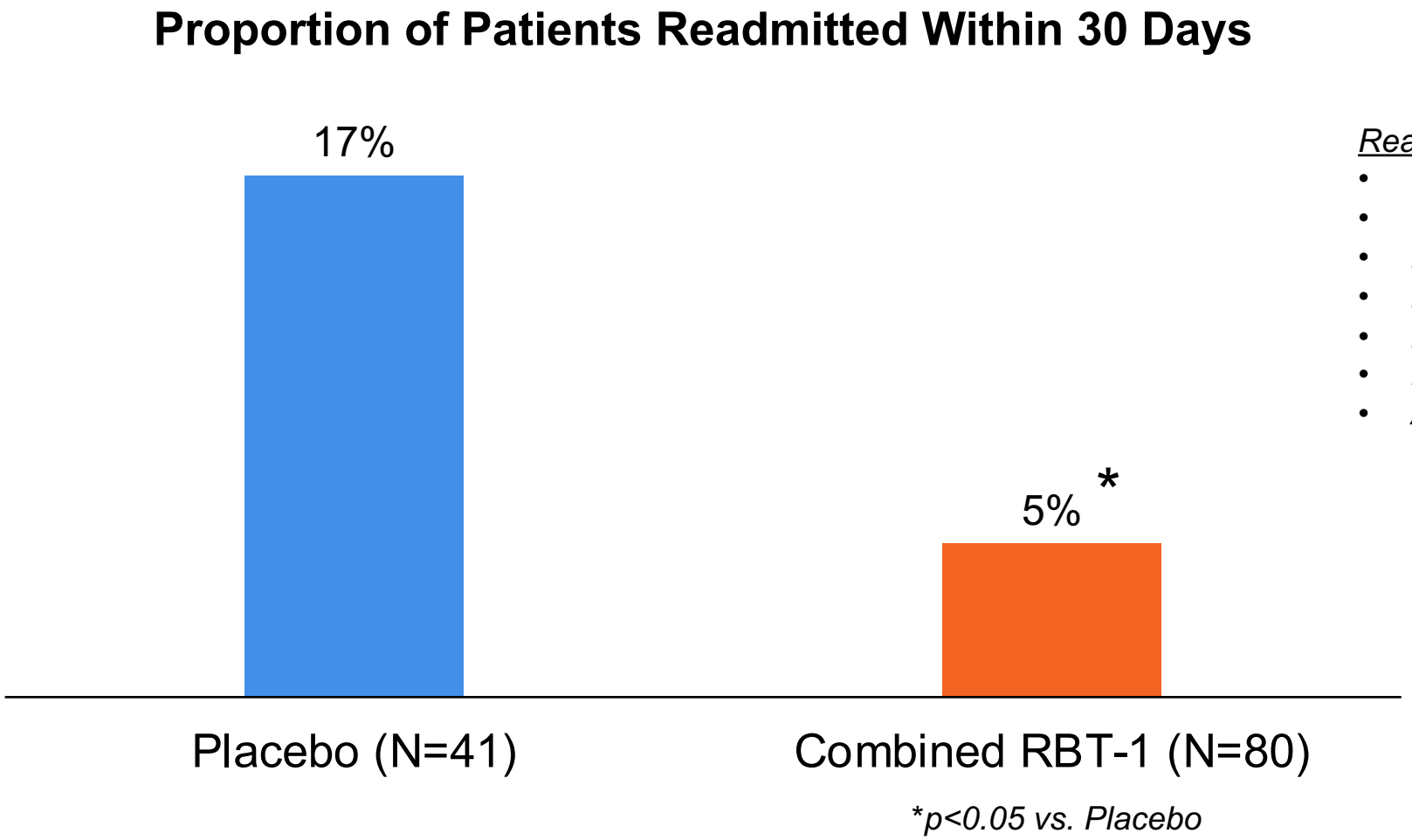
mITT Population



Excludes MV replacement/repair, ablations, septal myectomies

Statistically Significant Decrease in 30-Day Cardiopulmonary Readmission Rates in Patients Treated with RBT-1

mITT Population



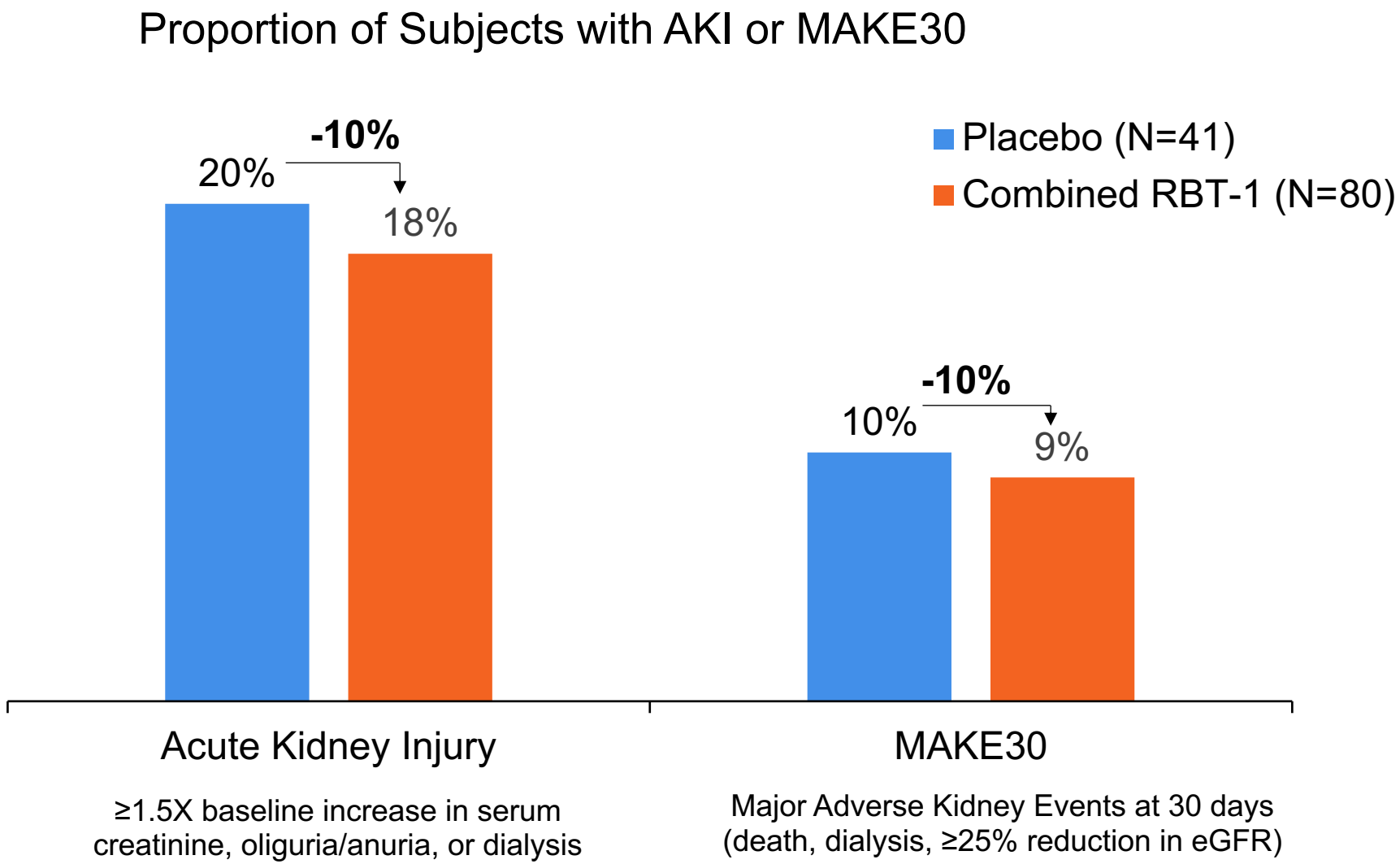
Readmissions were due to:

- *CHF/Worsening CHF*
- *Worsening pulmonary hypertension*
- *Pleural effusion/Worsening pleural effusion*
- *Pericardial effusion*
- *Post-cardiotomy syndrome*
- *Pulmonary emboli*
- *Acute respiratory failure*

**p<0.05 vs. Placebo*

Rates of AKI and MAKE30 (study population was not enriched for AKI events)

mITT Population



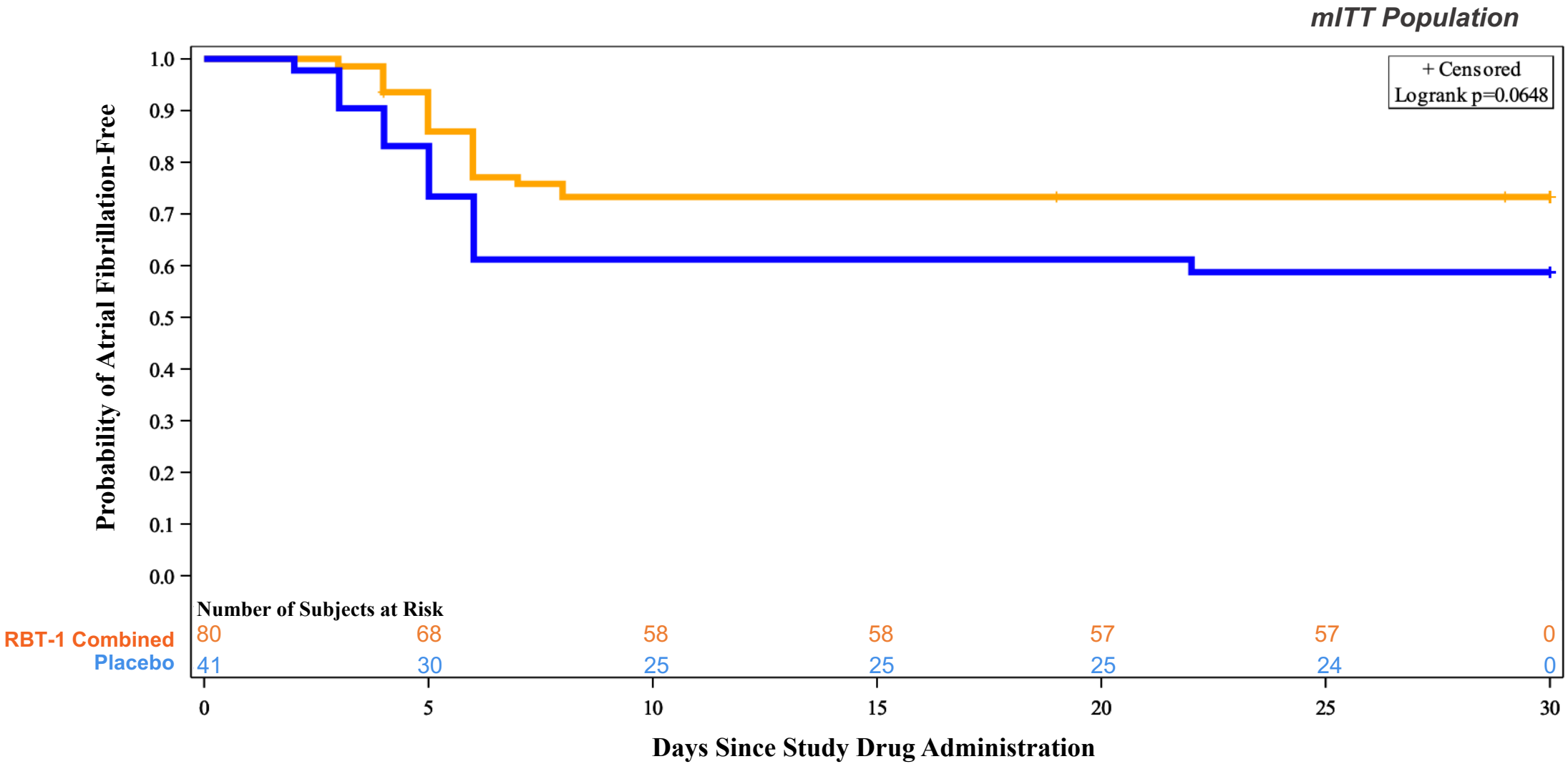
Clinical Events of Interest (as reported by Investigators)

mITT Population

	Placebo (N=41)	Combined RBT-1 (N=80)	LD (N=39)	HD (N=41)
Atrial Fibrillation, N (%)	17 (41.5)	21 (26.3)	11 (28.2)	10 (21.7)
Anemia, N (%)	11 (26.8)	11 (13.8)	6 (15.4)	5 (12.2)
Hypervolemia, N (%)	10 (24.4)	7 (8.8)	3 (7.7)	4 (9.8)

Topline Data

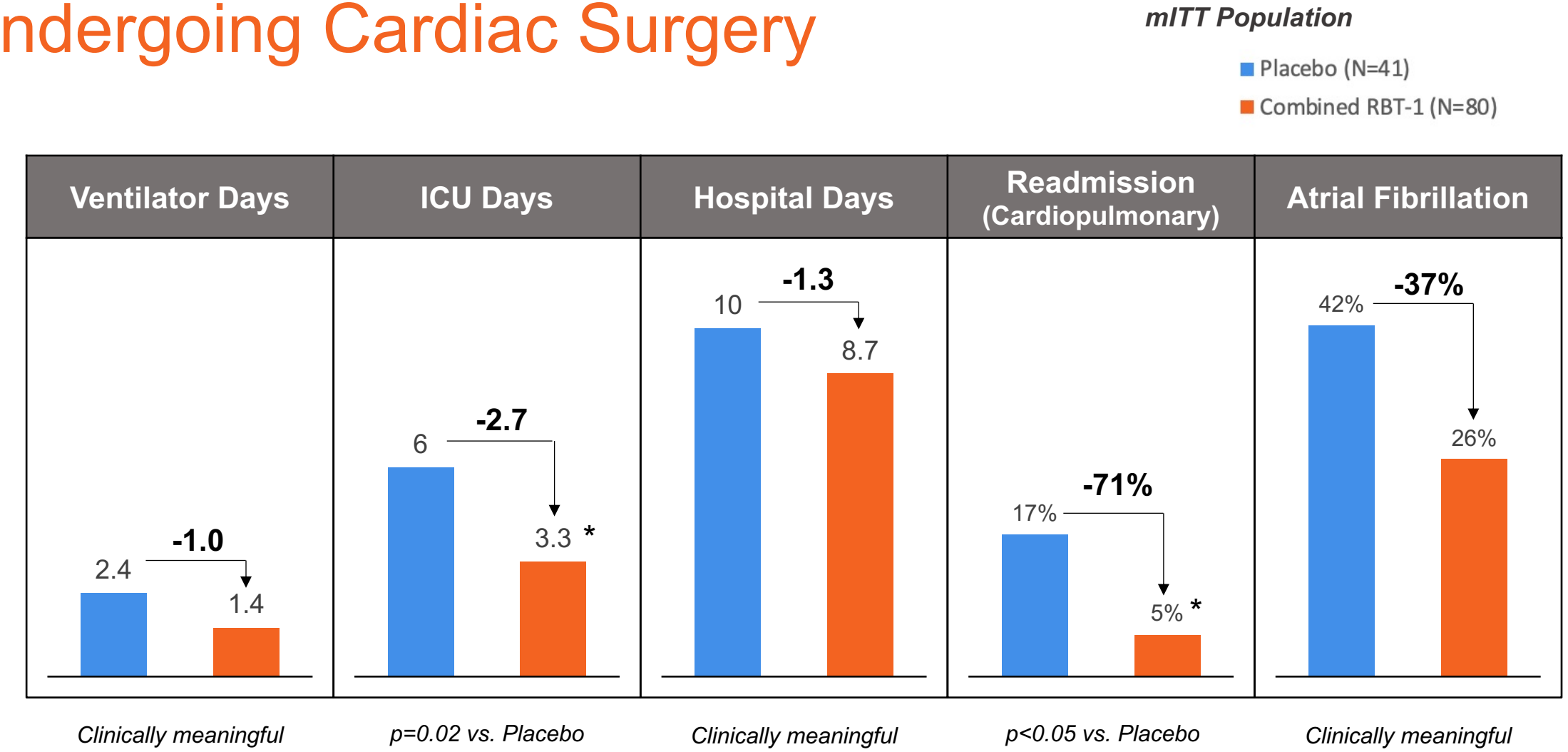
Time to Atrial Fibrillation



	Subjects	Event
RBT-1 Combined	80	21
Placebo	41	17

Topline Data

RBT-1 Improves Postoperative Outcomes in Patients Undergoing Cardiac Surgery



Topline Data

Composite Endpoint by Win Ratio – 6-Components

	HD+LD	Pbo	p-value (2-sided)
Death (%)	3.75	7.32	0.392
ICU Days (mean)	3.29	6.00	0.022
Vent Days (mean)	1.44	2.44	0.104
Atrial Fibrillation (%)	26.25	41.46	0.088
Readmission (%)	10.0	24.4	0.035
Hosp Days (mean)	8.7	9.97	0.801

	Died	ICU	Vent	AFib	Readmission	Hosp Days
Win	231	1554	26	104	43	54
Loss	114	932	13	69	17	88

	Win	Tie	Loss
Pairs	2012	35	1233

	Win Ratio	1-sided p-value
Result	1.634	0.017

Composite Endpoint by Win Ratio – 2-Components

	HD+LD	Pbo	p-value (2-sided)
ICU Days (mean)	3.28	6.00	0.0224
Readmission (%)	10	24.4	0.0352

	ICU	Readmission
Win	1810	96
Loss	998	39

	Win	Tie	Loss
Pairs	1906	337	1037

	Win Ratio	1-sided p-value
Result	1.8379	0.008

Topline Data

Overview of Adverse Events (AEs)

Safety Population

	Placebo (N=44)	Combined RBT-1 (N=91)	LD (N=45)	HD (N=46)
Subjects with any AE	40 (90.9)	83 (91.2)	39 (86.7)	44 (95.7)
Mild	7 (15.9)	26 (28.6)	11 (24.4)	15 (32.6)
Moderate	18 (40.9)	34 (37.4)	17 (37.8)	17 (37.0)
Severe	15 (34.1)	23 (25.3)	11 (24.4)	12 (26.1)
Subjects with at least one Serious AE	18 (40.9)	35 (38.5)	13 (28.9)	22 (47.8)
Subjects Discontinued due to AE	0	0	0	0
Died on Study	3 (6.8)	3 (3.3)	1 (2.2)	2 (4.3)
Cause of Deaths	• Sepsis • Stroke • Cardiac arrest		• Acute respiratory failure	• Cardiogenic shock • CO2 retention from chronic lung disease

Overview of most frequent Adverse Events

Safety Population

	Placebo (N=44)	Combined RBT-1 (N=91)	LD (N=45)	HD (N=46)
Subjects with at least one AE	40 (90.9)	83 (91.2)	39 (86.7)	44 (95.7)
Atrial Fibrillation	17 (38.6)	21 (23.1)	11 (24.4)	10 (21.7)
Hypotension	12 (27.3)	26 (28.6)	12 (26.7)	14 (30.4)
Pleural effusion	11 (25.0)	23 (25.3)	11 (24.4)	12 (26.1)
Atelectasis	10 (22.7)	22 (24.2)	11 (24.4)	11 (23.9)
Nausea	9 (20.5)	22 (24.2)	9 (20.0)	13 (28.3)
Procedural pain	11 (25.0)	18 (19.8)	9 (20.0)	9 (19.6)
Anemia	11 (25.0)	14 (15.4)	8 (17.8)	6 (13.0)
Hypervolemia	10 (22.7)	9 (9.9)	4 (8.9)	5 (10.9)
Acute kidney injury	6 (13.6)	12 (13.2)	8 (17.8)	4 (8.7)

Topline Data

Adjudicated Photosensitivity Events

Safety Population

Photosensitivity AEs Adjudicated	Placebo (N=44)	LD (N=45)	HD (N=46)
Photosensitivity, N (%)	0	4 (9)	10 (22)
Day of Onset Post-Infusion, Median Days	--	2.0	2.0
Time to Resolution, Median Days	--	3.5	8.0

Summary: RBT-1 Phase 2 Preliminary Topline Data

- Statistically significant increase in biomarkers of cytoprotective preconditioning (primary endpoint; $p<0.0001$)
- Statistically significant reduction in ICU days (2.7 days; $p=0.02$) and 30-day cardiopulmonary readmission rates (-71%, $p<0.05$)
- Clinically meaningful reduction in ventilator time (1 day) and hospital length of stay (1.3 days)
- Clinically meaningful reduction in atrial fibrillation (-37%) and troponin I levels (-61%)
- Statistically significant benefit in composite outcomes (6 components, $p=0.02$)

THANK YOU

US, Canadian, and Australian sites interested in participating in the Phase 3 trial of RBT-1 please contact: alamy1@mac.com or bsingh@renibus.com

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