A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Multi-Center Trial of RBT-1 Evaluating Cytoprotective Biomarkers & Post-Operative Outcomes in Patients Undergoing Elective Coronary Artery Bypass Graft and/or Valve Surgery on Cardiopulmonary Bypass

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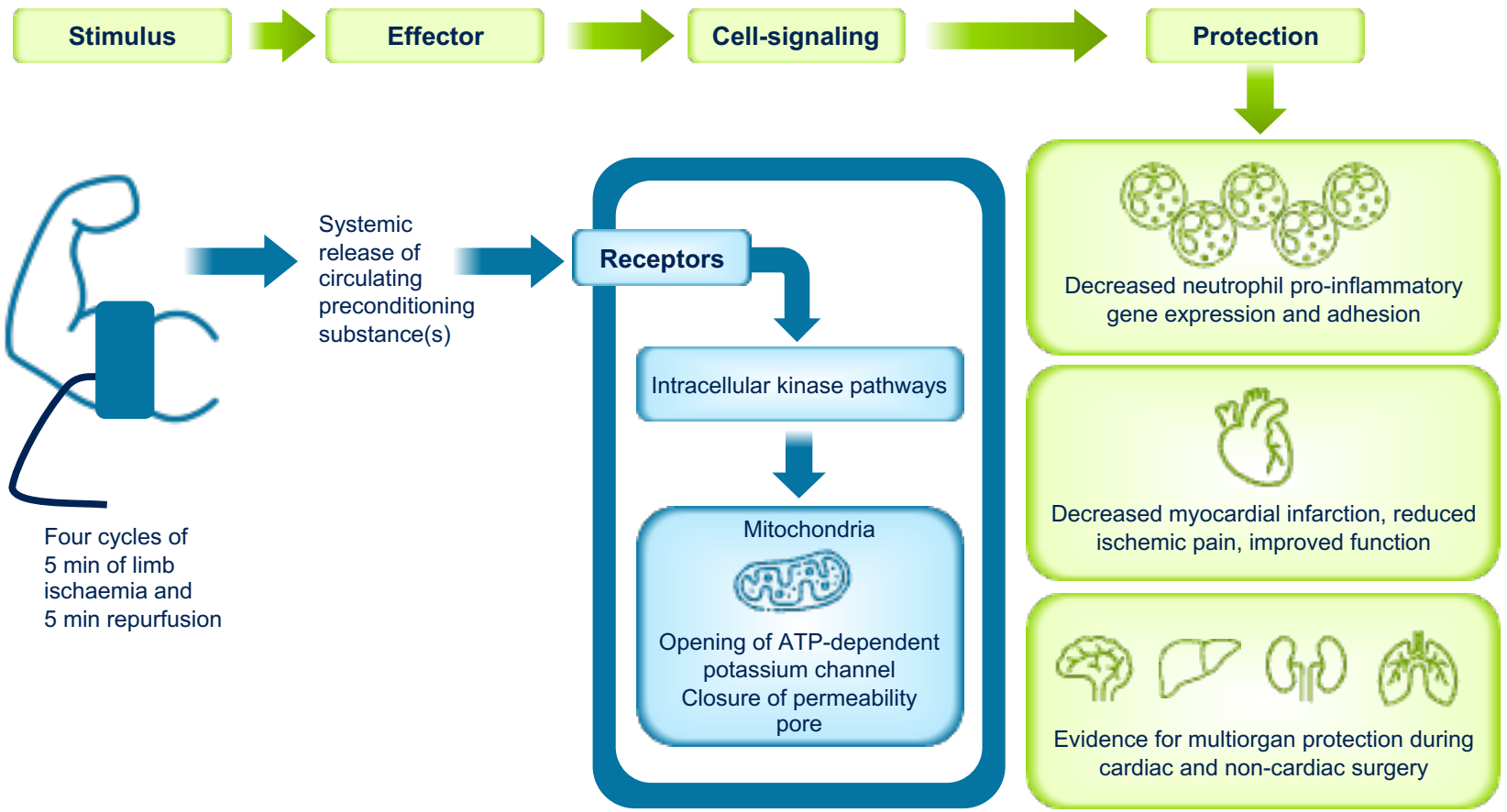
On behalf of START investigators

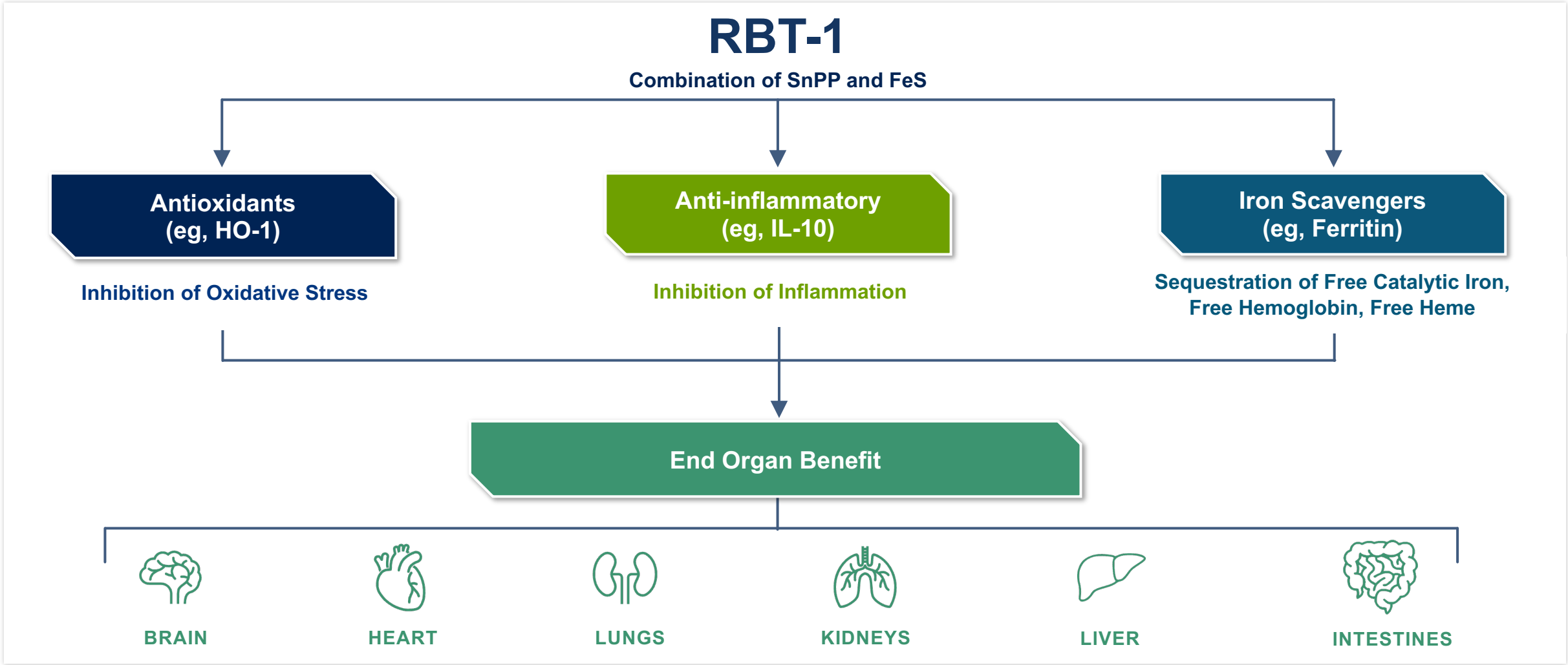
AATS – May 7, 2023

Preconditioning as a Means for Multi-Organ Protection



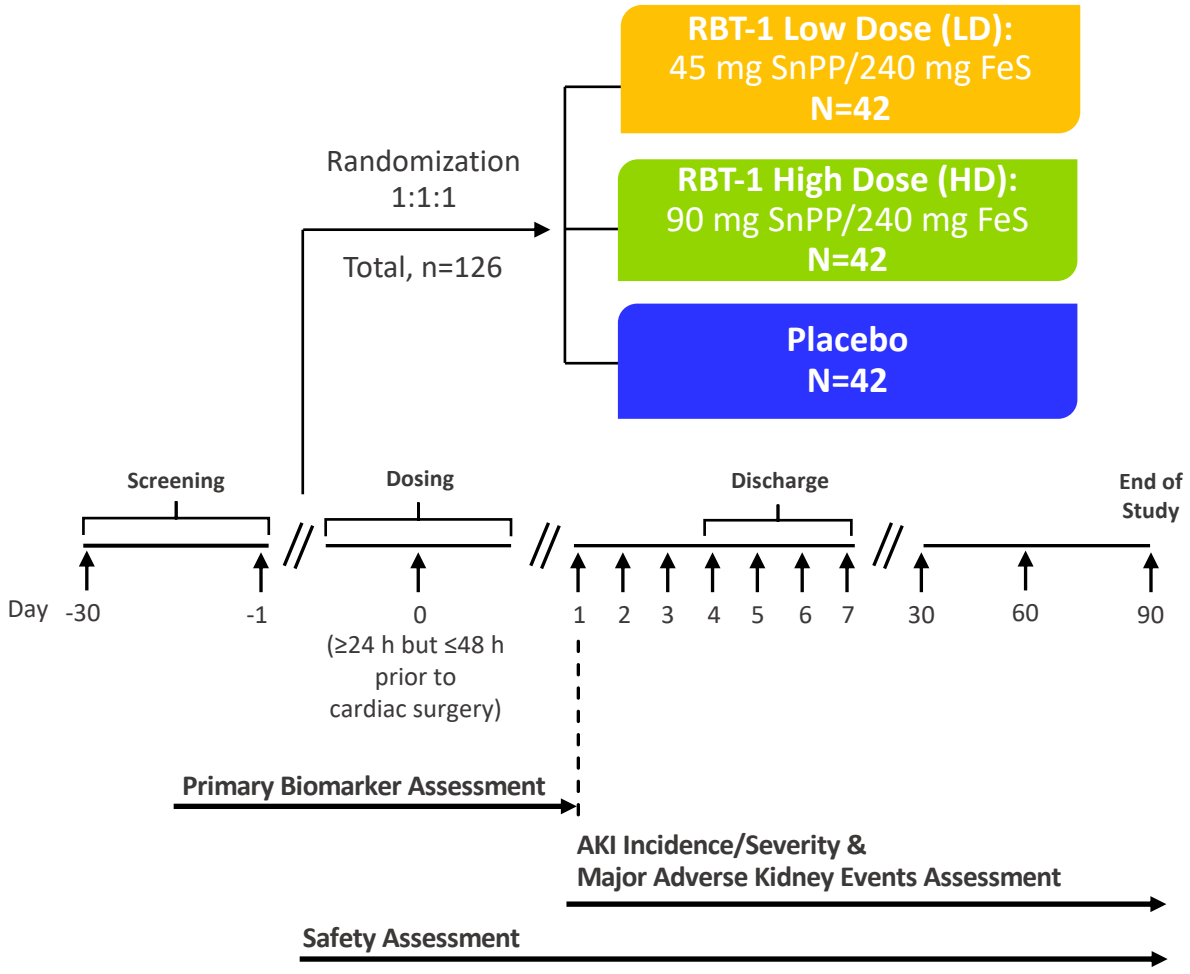
- Preconditioning elicits a protective response to surgery
- As early as 1929, it was observed that the kidneys of animals previously exposed to (preconditioned by) various minor stressors acquired resistance to organ failure
- In the early 1990s, remote ischemic preconditioning (RIPC), which involves a brief induction of ischemia and reperfusion to distal tissues using a sphygmomanometer in the upper arm or leg, was introduced

RBT-1 – Pharmacologic Approach to Preconditioning



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)



Primary Objective

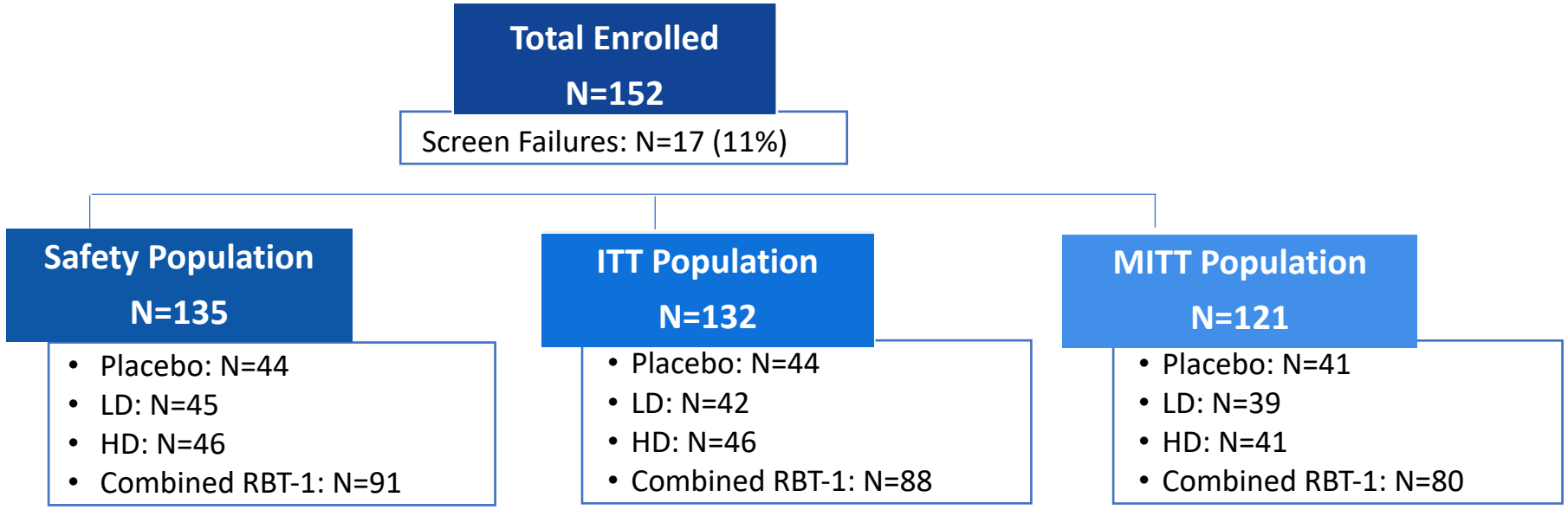
Effect of RBT-1 in generating a preconditioning response, measured by a composite of plasma biomarkers (heme oxygenase-1 [HO-1], ferritin, and interleukin-10 [IL-10]) from Baseline (pre-dose) through Day 1 pre-surgery.

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)
- 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 were eligible for primary endpoint assessment (ie, had biomarker assessments performed at Baseline and prior to surgery)
- **MITT population:** All subjects in the ITT population who underwent cardiac surgery without delay

Demographics Were Generally Balanced Across All Groups

MITT Population

	Placebo (N=41)	Low Dose (N=39)	High Dose (N=41)
Mean Age (yrs)	65 (19, 81)	65 (46, 82)	67 (37, 86)
Sex			
Female, N (%)	11 (27)	11 (28)	9 (22)
Male, N (%)	30 (73)	28 (72)	32 (78)
Race			
American Indian or Alaska Native, N (%)	0	0	1 (2)
Black, N (%)	2 (5)	4 (10)	1 (2)
Asian, N (%)	1 (2)	1 (3)	2 (5)
White, N (%)	38 (93)	32 (82)	37 (90)
Other, N (%)	0	2 (5)	0
Weight (kg), Mean (min, max)	89 (64, 132)	98 (51, 142)	91 (57, 150)
BMI (kg/m^2), Mean (min, max)	30 (19, 45)	33 (18, 48)	30 (20, 49)

Baseline Characteristics Were Generally Balanced Across All Groups

MITT Population

	Placebo (N=41)	Low Dose (N=39)	High Dose (N=41)
EuroScore, Mean (Min, Max)	2.1 (1, 10)	2.8 (1, 17)	2.4 (1, 9)
Low Risk (< 3), N (%)	35 (85)	31 (80)	31 (76)
Medium Risk (3 to 6), N (%)	4 (10)	3 (8)	8 (20)
High Risk (≥ 6), N (%)	2 (5)	5 (13)	2 (5)
≥3 AKI Risk Factors,* N (%)	7 (17)	11 (28)	13 (32)
Time of Infusion Before Surgery			
Mean (hrs)	38.6	38.6	38.4
Surgery Type			
CABG Alone, N (%)	20 (49)	20 (51)	24 (59)
Valve Alone, N (%)	7 (17)	13 (33)	9 (22)
CABG + Valve, N (%)	14 (34)	6 (15)	8 (20)
Duration of Surgery			
Mean (hrs)	4.9	5.0	4.9
Time on Pump			
Mean (hrs)	1.9	2.0	2.0

**AKI risk factors are comprised of: combined valve/CABG surgery, previous cardiac surgery with sternotomy, NYHA III/IV within 1 year prior to surgery, LVEF ≤35%, congestive heart failure, diabetes mellitus requiring insulin, diabetes mellitus with albuminuria, per-operative anemia, current hospitalization for cardiac or pulmonary disease, CKD Stage 3, CKD Stage 4, ≥65 years of age; each risk factor was assigned a score of 1 with CKD Stage 4 assigned a risk factor of 2*

Statistically Significant Increase in Cytoprotective Response Biomarkers with Both Low Dose and High Dose RBT-1

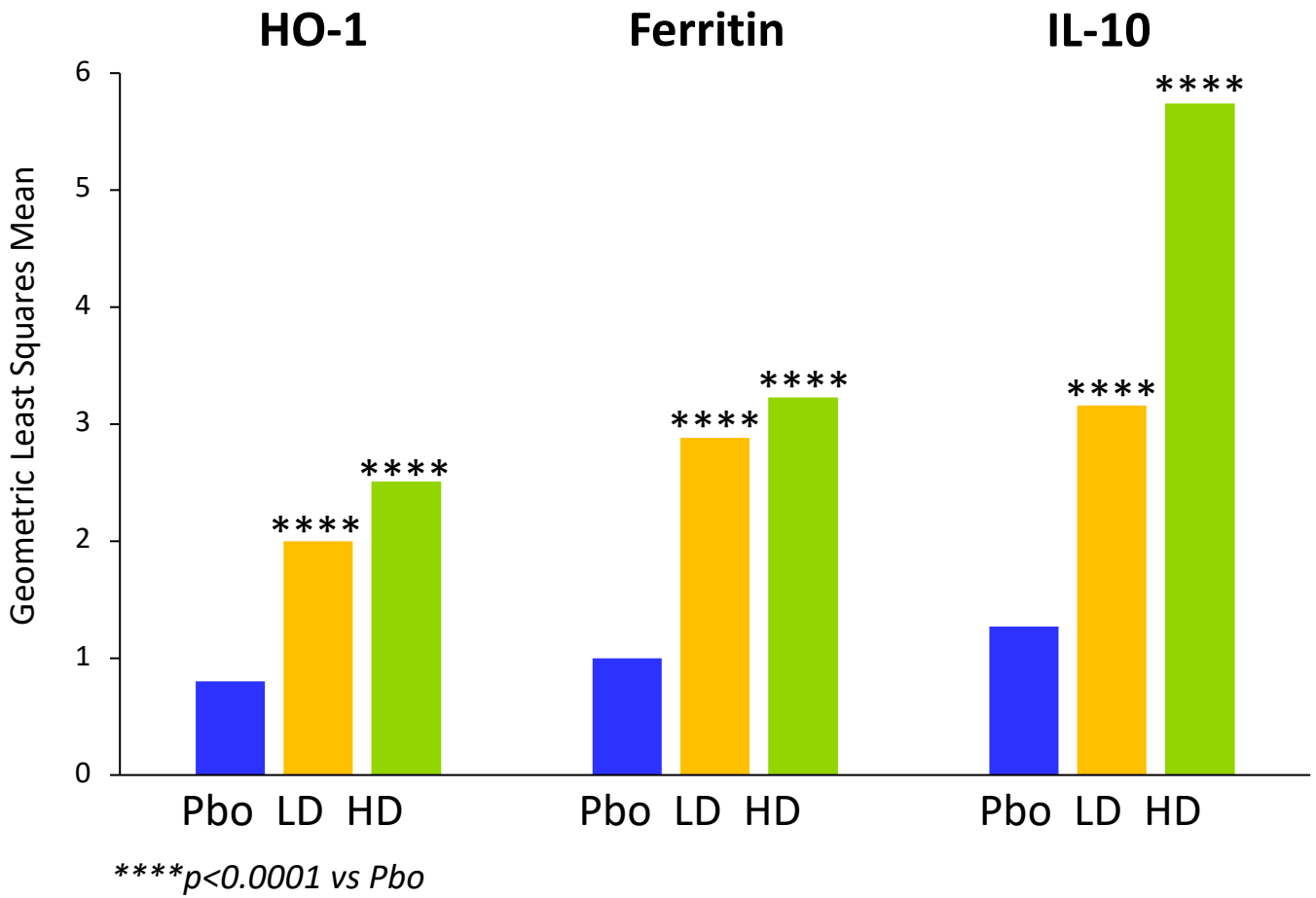
– Primary Endpoint Met –

ITT Population

Composite Biomarker Response

	Placebo (N=44)	Low Dose (N=42)	High Dose (N=46)
Mean*	1.00	2.63	3.60
P-value vs Pbo		<0.0001	<0.0001

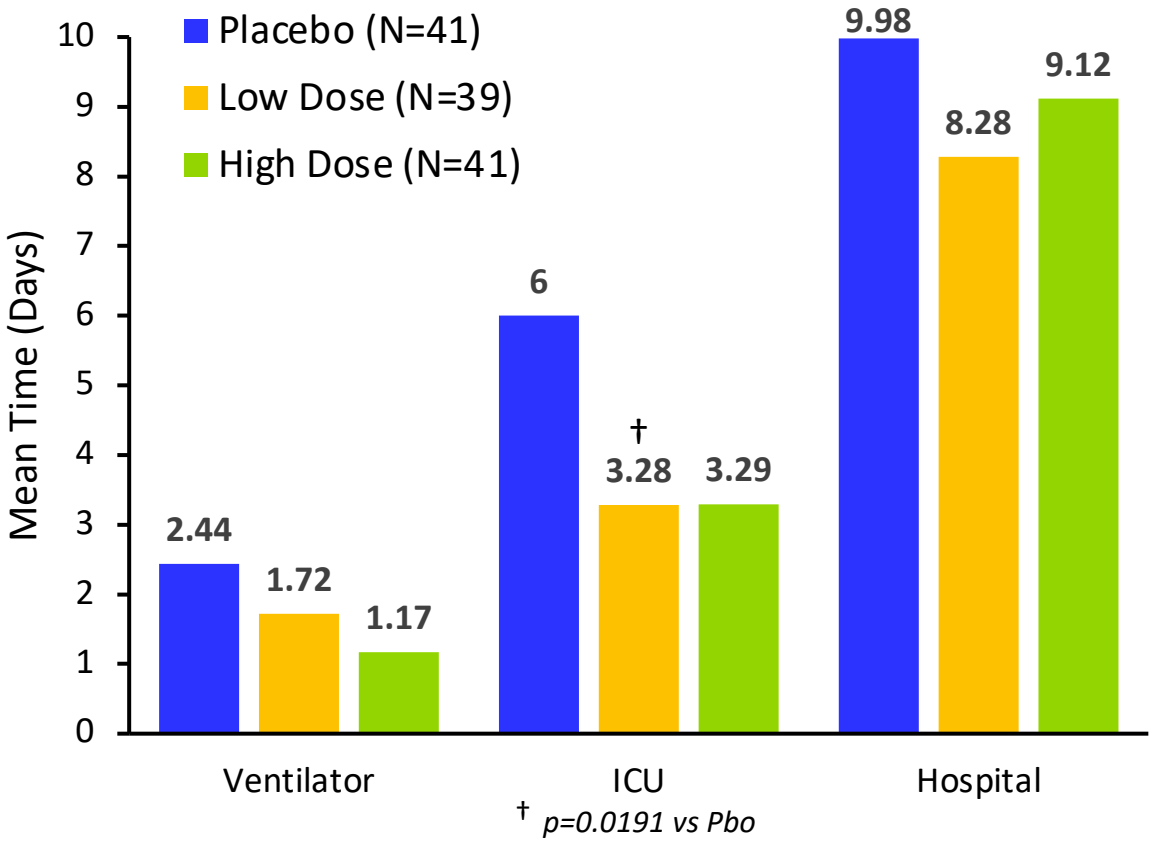
**Geometric least squares mean (GLSM) of the ratio of max Pre-Op value over Baseline*



*****p<0.0001 vs Pbo*

Statistically Significant Decrease in ICU Days and Clinically Meaningful Improvement in Clinical Outcomes

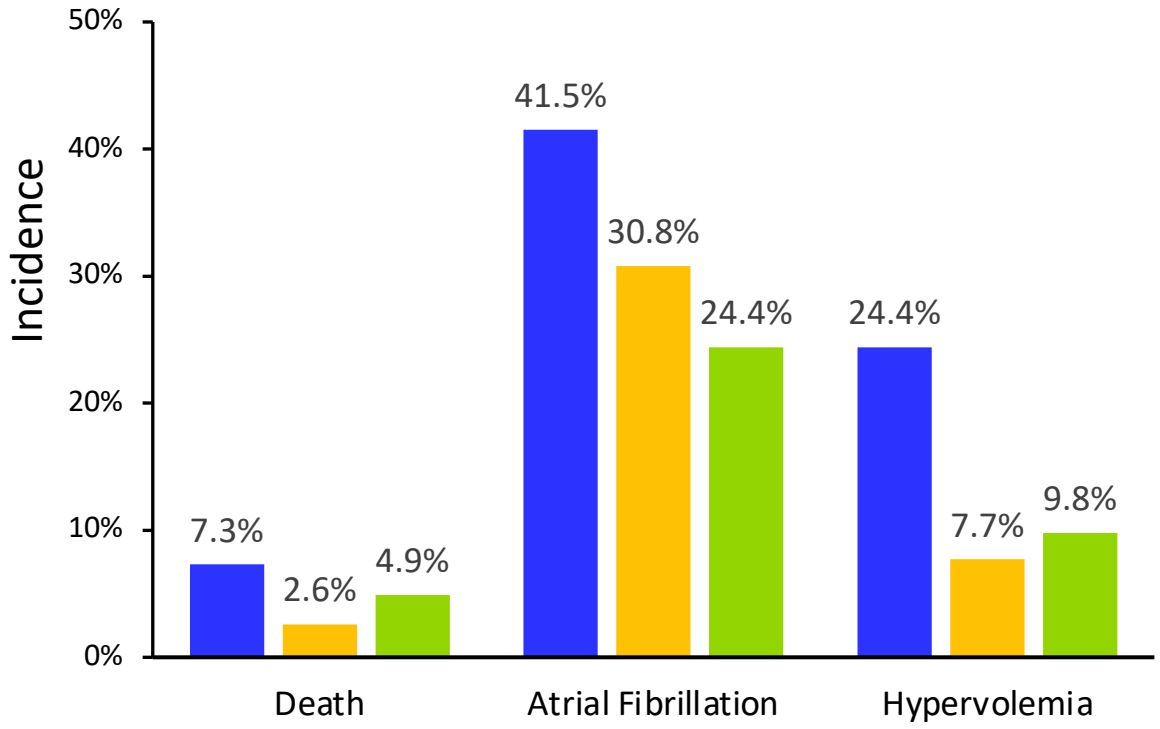
MITT Population



† *p=0.0191 vs Pbo*

Relative Risk Reduction vs Placebo

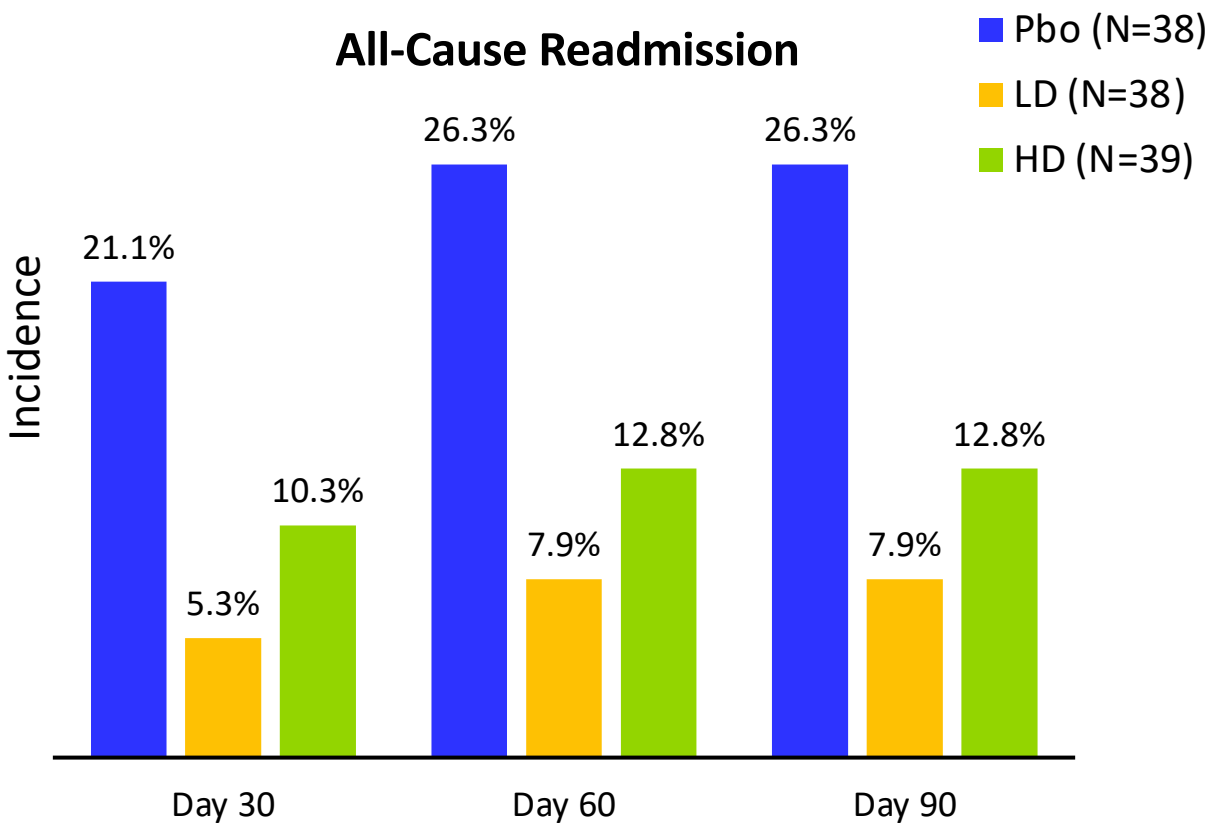
	Ventilator Days	ICU Days	Hospital Days
Low Dose	-30%	-45%	-17%
High Dose	-52%	-45%	-9%



Relative Risk Reduction vs Placebo

	Death	Atrial Fibrillation	Hypervolemia
Low Dose	-65%	-26%	-68%
High Dose	-33%	-41%	-60%

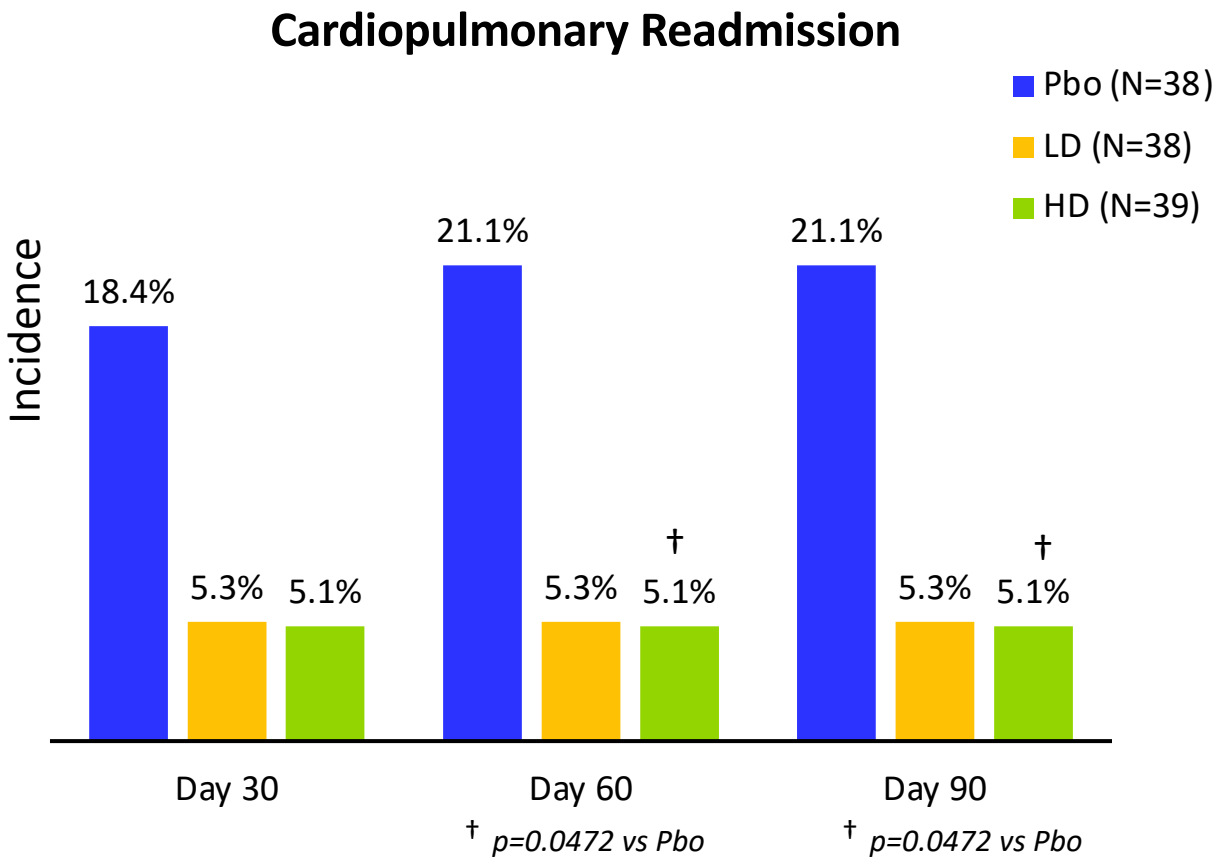
All-Cause Readmission Rates Improved with RBT-1, Continuing Through Day 90



	Relative Risk Reduction vs Placebo		
	Day 30	**Day 60**	**Day 90**
Low Dose	-75%	-70%	-70%
High Dose	-51%	-51%	-51%

MITT Population

Cardiopulmonary Readmission Rates Improved with RBT-1, Continuing Through Day 90

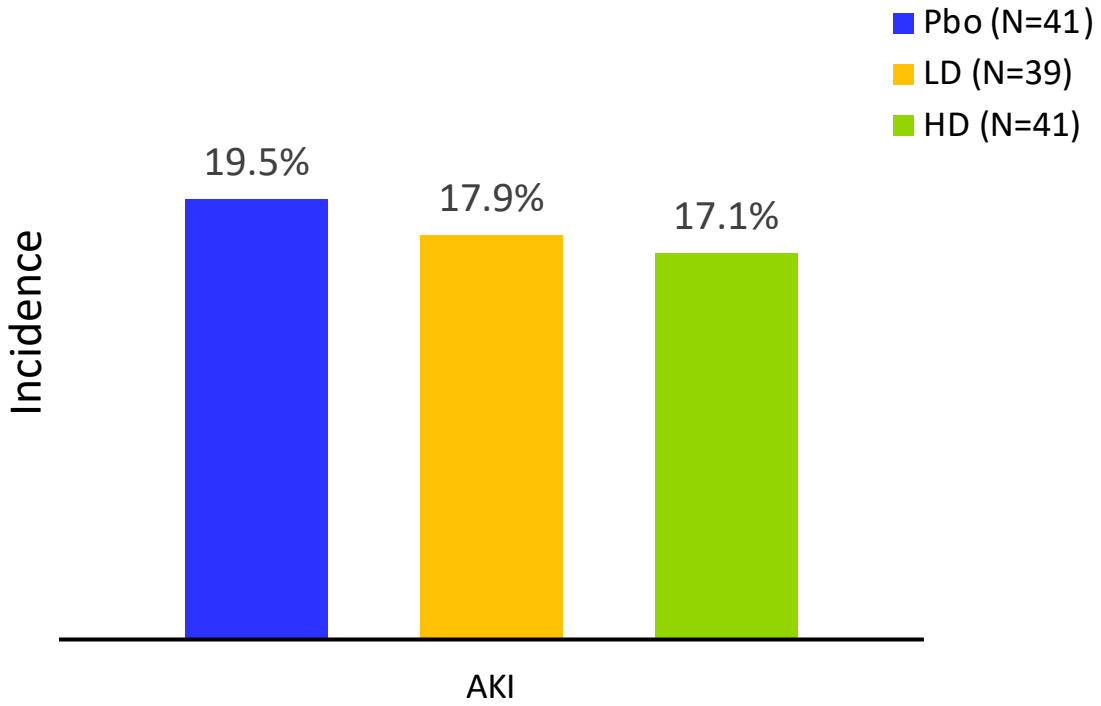


	Relative Risk Reduction vs Placebo		
	Day 30	**Day 60**	**Day 90**
Low Dose	-71%	-75%	-75%
High Dose	-72%	-76%	-76%

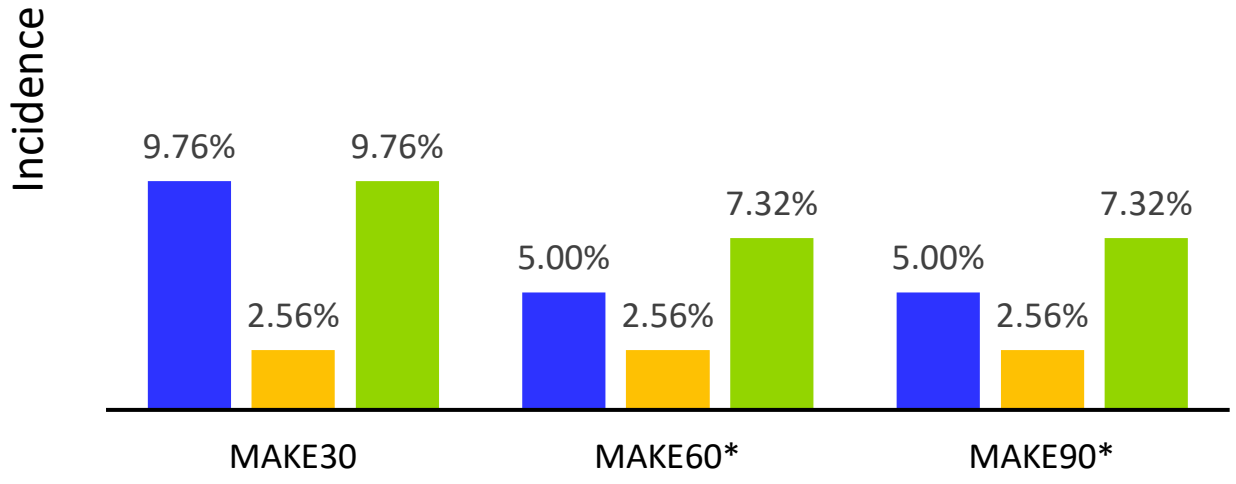
MITT Population

AKI & MAKE30/60/90 Rates Were Lower Overall Due to the Unenriched Population

MITT Population



	Pbo	LD	HD
≥3 AKI Risk Factors,* N (%)	7 (17)	11 (28)	13 (32)

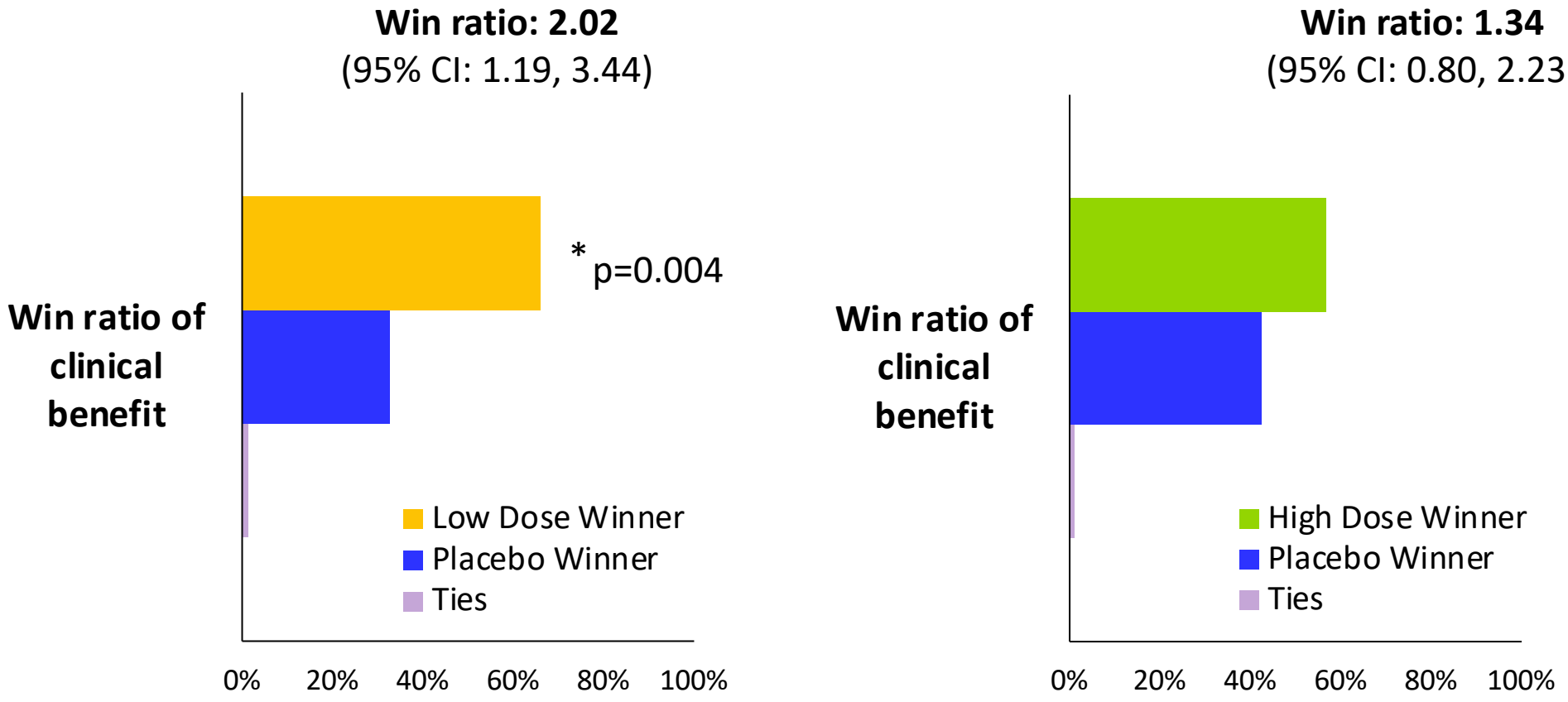


Relative Risk Reduction vs Placebo

	AKI	MAKE30	MAKE60	MAKE90
Low Dose	-8%	-74%	-49%	-49%
High Dose	-13%	0%	+46%	+46%

A Post-Hoc analysis of a Severity-Based Hierarchical Composite of Clinical Outcomes (Win Ratio) Showed Clinical Benefit with RBT-1

MITT Population



Win ratio derived from rank order analysis of death, AKI requiring dialysis, ICU days, 30-day cardiopulmonary readmission, atrial fibrillation, and hospital length of stay

Win ratio analysis is based on Finkelstein-Schoenfeld (F-S) method

Overview of Treatment-Emergent Adverse Events (TEAEs)

Safety Population

	Placebo (N=44)	Low Dose (N=45)	High Dose (N=46)
Subjects with any TEAE	40 (90.9)	40 (88.9)	44 (95.7)
Maximum Severity of Mild	7 (15.9)	12 (26.7)	15 (32.6)
Maximum Severity of Moderate	18 (40.9)	17 (37.8)	17 (37.0)
Maximum Severity of Severe	15 (34.1)	11 (24.4)	12 (26.1)
Subjects with at least one Treatment-Related TEAE	6 (13.6)	12 (26.7)	18 (39.1)
Excluding Adjudicated Photosensitivity	6 (13.6)	6 (13.3)	8 (17.4)
Subjects with at least one Serious TEAE	18 (40.9)	13 (28.9)	22 (47.8)
Subjects Discontinued due to TEAE	0	0	0
Died on Study	3 (6.8)	1 (2.2)	2 (4.3)
Cause of Deaths	• Sepsis • Stroke • Cardiac arrest	• Acute respiratory failure	• Cardiogenic shock • CO2 retention from chronic lung disease

Photosensitivity Adverse Events Were Dose-Dependent, with Early Onset and Resolution

Safety Population

Photosensitivity Adverse Events (AEs)	Placebo (N=44)	LD (N=45)	HD (N=46)
Photosensitivity, N (%)	--	6 (13.3)	12 (26.1)
Onset Post-Infusion, Median (Days)	--	2.5	2.0
Time to Resolution, Median (Days)	--	3.5	7.0

- Photosensitivity is a known side effect of SnPP (a metalloporphyrin)
  - Transient and generally mild to moderate in intensity
  - Sunblock can be used to prevent/reduce occurrence
- 3 surgeries were postponed due to Photosensitivity
  - All occurred in the high dose group
  - All subjects were exposed to the sun for a prolonged period of time post-infusion

Summary: RBT-1 Phase 2 Study

- Statistically significant upregulation of preconditioning response
- Consistent trends in improvement in clinical outcomes with RBT-1 treatment
- Post-hoc win ratio based on rank order of severity in clinical outcomes showed statistically significant improvement with LD RBT-1
- RBT-1 is well tolerated; primary drug-related AE is limited to transient, mild/moderate photosensitivity
- A Phase 3 study of RBT-1 will start soon

Thank you!