Effects of RBT-1 on preconditioning response biomarkers in patients undergoing coronary artery bypass graft or heart valve surgery: a multicentre, double-blind, randomised, placebo-controlled phase 2 trial

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Summary

Background RBT-1 is a combination drug of stannic protoporfin (SnPP) and iron sucrose (FeS) that elicits a preconditioning response through activation of antioxidant, anti-inflammatory, and iron-scavenging pathways, as measured by heme oxygenase-1 (HO-1), interleukin-10 (IL-10), and ferritin, respectively. Our primary aim was to determine whether RBT-1 administered before surgery would safely and effectively elicit a preconditioning response in patients undergoing cardiac surgery.

Methods This phase 2, double-blind, randomised, placebo-controlled, parallel-group, adaptive trial, conducted in 19 centres across the USA, Canada, and Australia, enrolled patients scheduled to undergo non-emergent coronary artery bypass graft (CABG) and/or heart valve surgery with cardiopulmonary bypass. Patients were randomised (1:1:1) to receive either a single intravenous infusion of high-dose RBT-1 (90 mg SnPP/240 mg FeS), low-dose RBT-1 (45 mg SnPP/240 mg FeS), or placebo within 24–48 h before surgery. The primary outcome was a preoperative preconditioning response, measured by a composite of plasma HO-1, IL-10, and ferritin. Safety was assessed by adverse events and laboratory parameters. Prespecified adaptive criteria permitted early stopping and enrichment. This trial is registered with ClinicalTrials.gov, NCT04564833.

Findings Between Aug 4, 2021, and Nov 9, 2022, of 135 patients who were enrolled and randomly allocated to a study group (46 high-dose, 45 low-dose, 44 placebo), 132 (98%) were included in the primary analysis (46 high-dose, 42 low-

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dose, 44 placebo). At interim, the trial proceeded to full enrollment without enrichment. RBT-1 led to a greater preconditioning response than did placebo at high-dose (geometric least squares mean [GLSM] ratio, 3.58; 95% CI, 2.91–4.41; p < 0.0001) and low-dose (GLSM ratio, 2.62; 95% CI, 2.11–3.24; p < 0.0001). RBT-1 was generally well tolerated by patients. The primary drug-related adverse event was dose-dependent photosensitivity, observed in 12 (26%) of 46 patients treated with high-dose RBT-1 and in six (13%) of 45 patients treated with low-dose RBT-1 (safety population).

Interpretation RBT-1 demonstrated a statistically significant cytoprotective preconditioning response and a manageable safety profile. Further research is needed. A phase 3 trial is planned.

Funding Renibus Therapeutics, Inc.

Keywords: Coronary artery bypass graft; CABG; Preconditioning response; Cardiopulmonary bypass; Heart valve; Acute kidney injury

Research in context

Evidence before this study

Despite extensive research on ischemic preconditioning as a cardioprotective strategy in the perioperative setting, a significant gap remains between experimental findings and clinical practice. Current meta-analyses of randomised controlled trials suggest that remote ischemic preconditioning does not reduce morbidity or mortality in patients undergoing cardiac surgery with cardiopulmonary bypass. RBT-1 is a novel pharmacological approach to preconditioning that is believed to activate organ–protective pathways, as measured by the plasma biomarkers heme oxygenase-1 (HO-1), interleukin-10 (IL-10), and ferritin. We performed a search in MEDLINE, from database inception until September 25, 2023, using the search terms "organ protection", "precondition", "CABG", "heart valve", and "cardiopulmonary bypass", to identify randomised studies in adults evaluating the impact of pharmacological preconditioning agents before coronary artery bypass graft (CABG) and/or heart valve surgery. Various pharmacological preconditioning strategies such as volatile anesthetics, noble gases, dexmedetomidine, and levosimendan, have been evaluated in randomised controlled trials in cardiac surgery with largely neutral results.

Added value of this study

In this international, double-blind, randomised controlled trial of 135 participants who were scheduled to undergo non-emergent CABG and/or heart valve surgery, both high-dose and low-dose RBT-1 demonstrated a statistically significant cytoprotective preconditioning response compared with placebo. The drug was well tolerated, with safety events limited to transient, dose-dependent photosensitivity.

Implications of all the available evidence

RBT-1 has the potential to improve post-operative complications in cardiac surgery, as well as in other surgeries where inflammation, oxidative stress, and the release of free catalytic iron trigger various post-operative complications. Further research is needed. A phase 3 trial is planned.

Introduction

Although significant advancements have been made in cardiac surgery, post-operative complications remain a major concern and often lead to adverse clinical outcomes for patients. In coronary artery bypass graft (CABG), heart valve, or combined CABG/heart valve surgery, approximately two-thirds of patients experience post-operative complications, including death, reoperation, stroke, prolonged ventilation, renal failure, atrial fibrillation, and 30-day readmission.[1,2] Cardiac surgery and cardiopulmonary bypass activate a systemic inflammatory response due to factors such as ischemia, blood contact with the cardiopulmonary bypass circuit, and reperfusion injury upon discontinuing cardiopulmonary bypass.[3,4] Inflammation, oxidative stress, and the release of free catalytic iron, collectively contribute to organ dysfunction and the development of complications that commonly occur after cardiac surgery.[5]

Ischemic preconditioning is an established cardioprotective phenomenon where brief episodes of ischemia and reperfusion applied before a longer coronary artery occlusion reduce myocardial infarct size.[6,7] However, randomised controlled trials (RCTs) of remotely applied ischemic preconditioning have yielded conflicting results in improving clinical outcomes for patients undergoing cardiac surgery.[8–10] Current meta-analyses suggest that remote ischemic preconditioning does not reduce morbidity or mortality in patients undergoing

cardiac surgery with cardiopulmonary bypass.[11] Pharmacological preconditioning is an attractive alternative approach that aims to mimic ischemic preconditioning by manipulating cytoprotective biochemical pathways to protect organs without inducing ischemia. Pharmacological preconditioning strategies in cardiac surgery such as volatile anesthetics,[12] noble gases,[13] dexmedetomidine,[14] and levosimendan,[15] have been evaluated in RCTS with largely neutral results. We apply the concept of ischemic preconditioning (i.e., cardioprotection) more broadly to multi-organ protection by activating cytoprotective pathways that are not organ specific. Cardiac surgery provides a unique opportunity to evaluate preconditioning treatments due to the known timing of surgery and cardiopulmonary bypass and the elevated risk of multi-organ dysfunction (e.g., acute kidney injury). Despite extensive research on pharmacological preconditioning as a 'cardioprotective' strategy in the perioperative setting, there remains a significant gap between experimental findings and clinical practice.[16,17] The IMproving Preclinical Assessment of Cardioprotective Therapies (IMPACT) criteria have been proposed to improve translation of novel interventions into clinical practice.[18] Novel pharmacological preconditioning interventions that can reduce the risk of complications with the potential to improve short- and long-term patient outcomes and reduce healthcare resource utilisation are needed.

RBT-1 is currently under development as a prophylactic drug designed to induce a preconditioning response in multiple organs to reduce the hypermetabolic consequences of surgery and cardiopulmonary bypass. RBT-1 is a combination drug comprised of stannic protoporfin (SnPP) and iron sucrose (FeS), which activate various cytoprotective antioxidant, anti-inflammatory, and iron-scavenging pathways. The activation of these pathways by RBT-1, as measured by the plasma biomarkers heme oxygenase-1 (HO-1), interleukin-10 (IL-10), and ferritin, is expected to have activity across multiple organ systems including the heart, lungs, kidneys, liver, and brain.[19–22] Within 24–48 h after a single intravenous infusion of RBT-1, preconditioning response biomarkers are activated in humans[23] and are believed to protect against organ damage in response to subsequent injury, such as cardiac surgery. Therefore, we investigated whether preoperative administration of RBT-1 would safely and effectively elicit a preconditioning response and improve clinical outcomes in patients undergoing CABG and/or heart valve surgery with cardiopulmonary bypass. Here, we report the results of our phase 2 trial with RBT-1.

Methods

Study design and participants

This was a phase 2, multicentre, double-blind, randomised, placebo-controlled, parallel-group, adaptive trial. In the statistical analysis plan, we prespecified that the trial may be carried out in two stages using a group sequential design with early stopping and patient enrichment permitted based on prespecified primary and secondary outcomes. Patients were enrolled from 19 centres in tertiary hospitals across the United States, Canada, and Australia from August 2021 to November 2022.

Participants were recruited using convenience sampling in selected hospitals by trained local study staff. Eligible participants were adults ≥18 years of age with stable kidney function who were scheduled to undergo non-emergent CABG and/or heart valve surgery with cardiopulmonary bypass. Key exclusion criteria were: estimated glomerular filtration rate ≤20 mL/min/1.73 m^2 or need for dialysis, intraoperative circulatory arrest or deep hypothermia, requirement for inotropes or vasopressors or other mechanical devices prior to surgery, active infection, and serum ferritin >500 ng/mL. Self-reported sex assigned at birth was collected as a binary variable.

Ethics

Institutional review board approval was obtained centrally (Advarra) or locally based on centre requirements, and informed consent was obtained from each patient before enrollment. The protocol was approved by the relevant health authorities and institutional review boards (date: November 6, 2020; project number: Pro00047629), and is available in the Supplementary Materials. The trial was registered on ClinicalTrials.gov (NCT04564833) prior to study enrollment and this study followed the Consolidated Standards of Reporting Trials (CONSORT) Harms 2022 and adaptive designs CONSORT extension reporting guidelines.[24,25] All participants provided written informed consent. Standard procedures were followed for handling and processing records as per Good Clinical Practice (GCP) and the data management standard operating procedures of the contract research organisation.

Randomisation and masking

Consenting patients fulfilling the eligibility criteria were randomised 1:1:1 to receive high-dose RBT-1, low-dose RBT-1, or placebo by the local pharmacy using an Interactive Response Technology (IRT) system. A biostatistician not otherwise involved in the conduct of the trial generated the random sequence, which was stratified by centre. The treatment allocation was provided directly to the local hospital pharmacy where the medication was prepared. The medication bag and intravenous line were masked to conceal the colour of the medication. Patients, study personnel, hospital staff involved in the care of the patients, and outcome assessors were masked to treatment allocation during the study. Operational bias was minimised using an independent statistician with confidential access to unblinded interim results.

Procedures

Patients assigned to high-dose RBT-1 received a single intravenous infusion of 90 mg SnPP and 240 mg FeS, while those assigned to low-dose RBT-1 received 45 mg SnPP and 240 mg FeS. The placebo group received an equal volume of normal saline. The SnPP doses were selected based on results from a previous phase 1 b study that evaluated several doses of SnPP (9 mg, 27 mg, 45 mg, 63 mg and 90 mg) with 240 mg FeS in healthy participants.[23] After observing statistically significant biomarker response at RBT-1 doses of 45 mg SnPP/240 mg FeS or more, the low dose for the current study was selected as 45 mg SnPP/240 mg FeS and the high-dose was selected as 90 mg SnPP/240 mg FeS. The plasma half-life for both SnPP and FeS is approximately 4–8 h, while the tissue half-life is likely to be a few weeks. Infusion of RBT-1 or placebo was administered over a 2-h period, between 24 and 48 h prior to surgery, to allow adequate time for the activation of a preoperative preconditioning response. Patients were followed daily through Day 7 (or hospital discharge, if earlier) and monthly through Day 90.

Outcomes

The prespecified primary composite outcome was a preconditioning response before surgery, measured by the upregulation of a composite of cytoprotective proteins (plasma HO-1, IL-10, and ferritin) and defined as the geometric least squares mean (GLSM) ratio of the maximum preoperative value over baseline (24–48 h before surgery) in the log scale, after anti-log transformation of each group separately. Values > 1 in the primary outcome indicate an increase in the preconditioning response compared with baseline.

Prespecified secondary outcomes included acute kidney injury (AKI), sustained reduction in urine output, and tubular injury biomarker response. AKI was defined as a 1.5x baseline increase (i.e., ≥50% increase) in serum creatinine; or documented adverse event (AE) of sustained reduction in urine output, oliguria, or anuria; or initiation of dialysis post-cardiac surgery through Day 5. Sustained reduction in urine output was defined as a reported AE of oliguria, anuria, or "sustained" reduction in urine output post-cardiac surgery through Day 5. Tubular injury biomarker response was the GLSM of the ratio of the maximum post-operative value over baseline for 3 kidney biomarkers (kidney injury molecule-1 [KIM-1], cystatin C, and neutrophil gelatinase-associated lipocalin [NGAL]) through Day 3. Due to emerging evidence after trial commencement, the protocol was amended to update the definition of secondary outcomes. In the amended protocol (version 5.0; Aug 25, 2022), the definition of AKI was made more stringent (updated from the modified Kidney Disease Improving Global Outcomes [KDIGO][26] criteria) and the definition of sustained reduction in urine output was made more specific (revised from simply "documented oliguria through Day 3").

Safety was assessed through AEs, serious AEs (SAEs), clinical laboratory parameters, physical examination, and vital signs. The primary drug-related AE was photosensitivity, a known reaction to the SnPP component of RBT-1. All AEs were systematically recorded on designated study case report forms for each participant beginning with the administration of investigational product and ending with the final study follow-up visit (Day 90). Comparisons of safety events between treatment groups were made post-hoc.

Other prespecified outcomes included ventilator, intensive care unit (ICU), and hospital days; readmission rates; and major adverse kidney events (MAKE) at Day 30 (MAKE30), Day 60 (MAKE60), and Day 90 (MAKE90). The MAKE outcome was defined as the occurrence of death, dialysis, or worsened kidney function (≥25% reduction in estimated glomerular filtration rate) assessed at 30, 60, and 90 days following an in-hospital AKI diagnosis.[27] Non-prespecified outcomes were reported from data systematically recorded on study case report forms during follow-up visits.

Sample size

The sample size calculation was based on the following values of the primary outcome derived from previous phase 1 studies of RBT-1 (mean ± SD): low-dose (1.07 ± 0.52), high-dose (1.30 ± 0.56), and placebo (0.19 ± 0.19). Assuming similar values to the previous studies, a sample size of 10 patients per group was estimated to provide >80% power for between-group comparisons (i.e., high-dose vs. placebo and low-dose vs. placebo) with a 2-sided $\alpha = 0.05$ significance level. For practical considerations, such as safety assessments required for proof-of-concept studies, an additional 32 patients per group were added to increase the total sample size to 126 patients (n = 42 per group).

Statistical analysis

The safety population in this study consisted of all randomised patients; the intent-to-treat (ITT) population consisted of those in the safety population who had primary biomarker measurements collected at baseline and prior to surgery, regardless of whether surgery occurred on time; and the modified intent-to-treat (MITT) population consisted of those in the ITT population who had surgery on time (i.e., 24–48 h post-infusion of study treatment). The primary outcome was evaluated in the ITT population, and all secondary and clinical outcomes were evaluated in the MITT population.

To compare the primary outcome between treatments and placebo groups, we undertook a prespecified primary analysis using an analysis of covariance (ANCOVA) model, in which treatment group was included as a main effect and surgery type and time on cardiopulmonary bypass (continuous) were included as covariates. The GLSM ratio (GLSM treatment group

over GLSM placebo group) was used to assess the relative change in the preconditioning biomarker response between groups (i.e., relative effect estimates). The secondary outcome of tubular injury biomarker response was analysed similarly to the primary outcome (i.e., the same covariates were used to refit the ANCOVA model) in a separate prespecified analysis. Secondary outcomes of AKI and sustained reduction in urine output were analysed using a Fisher's exact test. Unless otherwise specified, all between-group comparisons and confidence intervals used a 2-sided $\alpha = 0.05$ significance level. We summarised continuous variables as mean ± SD or median with interquartile range, where appropriate, and categorical variables using proportions.

For serum creatinine and estimated glomerular filtration rate, if the baseline pre-infusion value was missing and the corresponding local lab was not available, it was imputed with the screening local lab result. Biomarker values below the lower limit of quantification (LLOQ) were replaced by the LLOQ value divided by 2. Biomarker values above the upper limit of quantification (ULOQ) were replaced by the ULOQ value.

To control the overall type-I error rate of the primary outcome only, due to multiple comparisons between each active treatment and placebo, a gatekeeping procedure was used. Specifically, the high-dose RBT-1 group was compared to the placebo group first. The low-dose RBT-1 group was compared to the placebo group only if the p-value between the high-dose RBT-1 and placebo groups was <0.05. The type-I error rate was not controlled for any secondary outcomes.

A single prespecified interim analysis for efficacy (based mainly on the primary outcome) was planned after 60 patients (20 per group) completed the Day 30 assessments. The interim analysis of the primary outcome was conducted using the same methodology as the primary analysis at study completion. An independent statistician not involved in the conduct of the trial completed the interim analysis following the statistical analysis plan. Prespecified adaptive decision-making criteria were: 1) if a significant difference ($p \leq 0.05$) in the primary endpoint is observed between the active treatment and placebo groups, the study will be stopped unless further enrollment is needed to provide additional evidence in support of the secondary endpoints, 2) if a significant difference ($p \leq 0.05$) in the primary endpoint is not observed between the active treatment and placebo groups, enrollment will proceed to Stage 2 for another 20 patients per group, 3) if one of the active dose groups is dropped, the remaining active dose and placebo groups will continue into Stage 2 for another 30 participants per treatment group, and 4) the Stage 2 population may be enriched based on risk factor distributions in the interim analysis population. As the composite preconditioning biomarkers were being measured for the first time in patients undergoing cardiac surgery who were treated with RBT-1, it was not possible to plan all potential trial adaptations upfront. Therefore, the prespecified stopping rules were nonbinding and no type-I error adjustment was made for the group-sequential (i.e., 2-stage) design.

A post-hoc hierarchical composite analysis (win ratio), based on the Finkelstein-Schoenfeld method,[28,29] was conducted to assess the effect of RBT-1 on the hierarchical composite outcome of death > AKI requiring dialysis > ICU days >30-day cardiopulmonary readmission (> denotes the order of the win ratio hierarchy, which decreases from left to right). The win ratio method involves a comparison of each patient in an active treatment group with each patient in the placebo group to determine whether the active treatment patient had a better outcome (a "win"), a worse outcome (a "loss"), or an identical outcome (a "tie"). Each comparison begins with the death outcome and proceeds through the hierarchically ordered set of outcomes described above until the first outcome is identified for which the outcomes differ between the patients; this outcome is used to determine the "win" or "loss." The win ratio is the total number of wins divided by the total number of losses, and a win ratio >1 indicates better outcomes with active treatment. All analyses were performed using SAS software, version 9.4 (SAS Institute).

Role of the funding source

The funder of the study was involved in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Results

Between Aug 4, 2021, and Nov 9, 2022, 152 patients were enrolled at 19 centres across the USA, Canada, and Australia (Supplementary Table S1). Among the enrolled patients, 135 were randomly assigned to either the high-dose RBT-1 group (n = 46), low-dose RBT-1 group (n = 45), or placebo group (n = 44) (Fig. 1). The planned interim analysis was conducted from May 9 to June 6, 2022, and included the first 62 patients randomised (n = 20 high-dose, n = 19 low-dose, n = 23 placebo). The interim results indicated significant differences in the primary outcome between both high-dose RBT-1 ($p < 0.0001$) and low-dose RBT-1 ($p < 0.0001$) groups compared with the placebo group (Supplementary Table S2). The unblinded statistician recommended the study be continued without enrichment order to provide additional evidence in support of the secondary outcomes and the study sponsor representative agreed. Therefore, an additional 73 patients (approximately 24 per group) were enrolled without enrichment. The safety population consisted of all randomised patients (n = 135), all of whom received study treatment. Of those, 132 (98%) patients had biomarker measurements collected (ITT population), for whom the primary outcome was evaluated (n = 46 high-

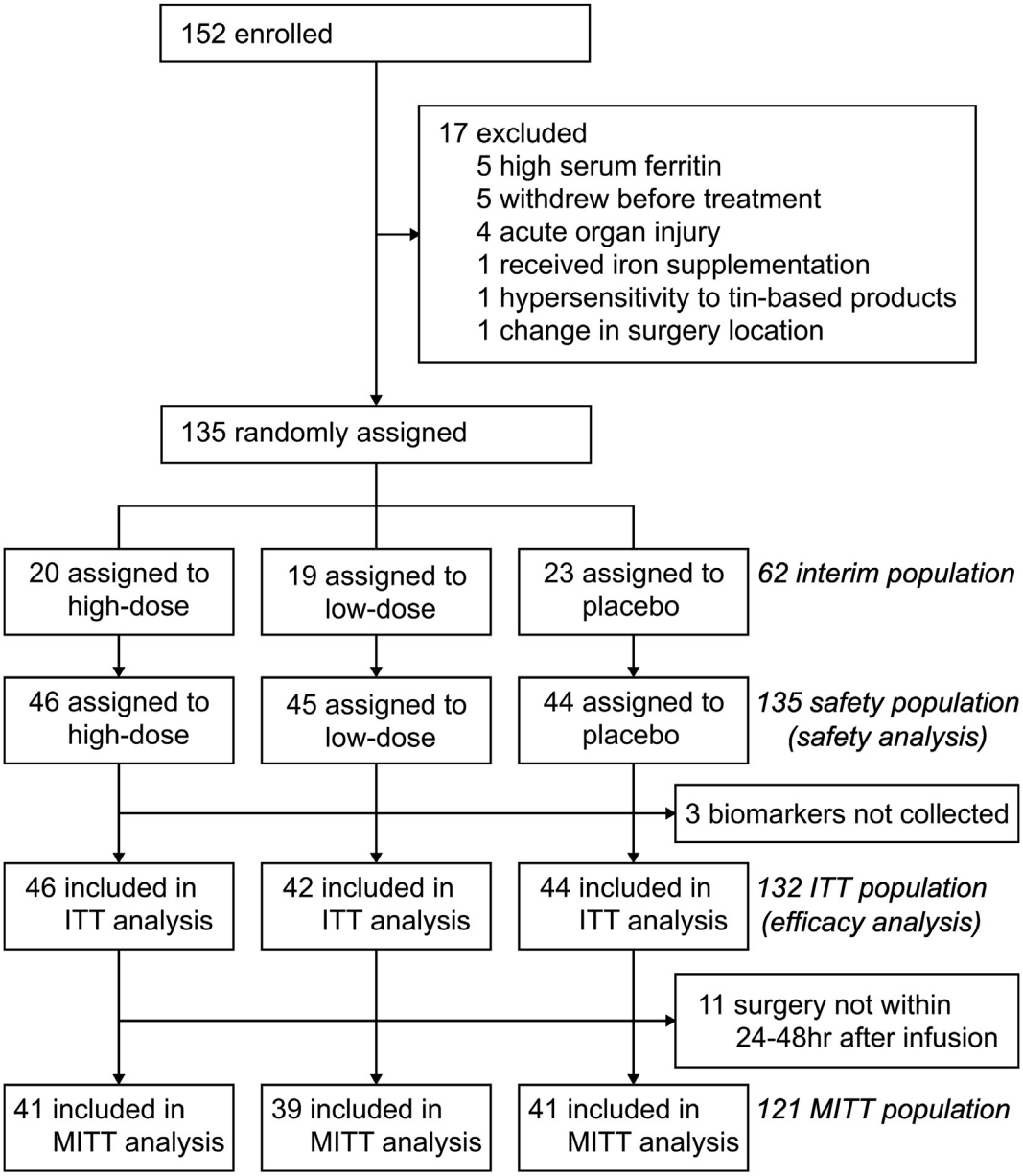

Fig. 1: **Enrollment and patient populations**. The total number of patients enrolled and randomised are shown. ITT = intent-to-treat. MITT = modified intent-to-treat.

dose, n = 42 low-dose, n = 44 placebo). From the ITT population, 121 patients had surgery on-time (24–48 h after infusion) and constituted the MITT population, for whom secondary and clinical outcomes were evaluated (n = 41 high-dose, n = 39 low-dose, n = 41 placebo).

At randomisation, baseline characteristics were generally similar among intervention groups in the safety population (Supplementary Table S3), ITT population (Table 1 and Supplementary Table S4), and MITT population (Supplementary Table S5). In the ITT population, the European system for cardiac operative risk evaluation (EuroSCORE) and AKI risk factors were often numerically lower in the placebo group vs. both RBT-1 groups. However, the contrary was observed for the incidence of combined surgery (CABG + Valve). The time between infusion and start of surgery, as well as time on cardiopulmonary bypass, were similar between the 3 treatment groups.

The primary composite outcome in the ITT population was 3.60 in the high-dose RBT-1 group, 2.63 in the

	High-dose (n = 46)	Low-dose (n = 42)	Placebo (n = 44)
Age, mean ± SD, years	66.0 ± 11.4	64.2 ± 8.6	65.7 ± 10.7
Sex			
Female	10 (22%)	11 (26%)	12 (27%)
Male	36 (78%)	31 (74%)	32 (73%)
Race			
White	41 (89%)	35 (83%)	41 (93%)
Black	2 (4%)	4 (10%)	2 (5%)
Asian	2 (4%)	1 (2%)	1 (2%)
American Indian	1 (2%)	0 (0%)	0 (0%)
Other	0 (0%)	2 (5%)	0 (0%)
Country			
United States of America	33 (72%)	30 (71%)	31 (70%)
Canada	8 (17%)	9 (21%)	10 (23%)
Australia	5 (11%)	3 (7%)	3 (7%)
Weight, mean ± SD, kg	91.1 ± 19.6	97.5 ± 20.9	90.3 ± 18.9
Body mass index, mean ± SD, kg/m^2	30.3 ± 6.6	32.5 ± 6.3	30.0 ± 5.8
EuroSCORE II, median (IQR)	1.7 (1.1–2.7)	1.2 (0.9–2.7)	1.5 (0.9–2.3)
Low Risk (<3)	35 (76%)	33 (79%)	36 (84%)
Medium Risk (3–6)	9 (20%)	4 (10%)	5 (12%)
High Risk (≥6)	2 (4%)	5 (12%)	2 (5%)
Acute kidney injury risk factors			
Age ≥65 years	28 (61%)	24 (57%)	26 (59%)
Diabetes mellitus requiring insulin	8 (17%)	7 (17%)	4 (9%)
Congestive heart failure	7 (15%)	6 (14%)	7 (16%)
Heart failure (NYHA III/IV) within 1 year prior to surgery	6 (13%)	3 (7%)	3 (7%)
Previous cardiac surgery with sternotomy	1 (2%)	1 (2%)	0 (0%)
Left ventricular ejection fraction ≤35%	5 (11%)	6 (14%)	2 (5%)
Estimated glomerular filtration rate ≥20 to < 60 mL/min/1.73 m^2	13 (28%)	13 (31%)	8 (18%)
Preoperative anaemia (haemoglobin <10 g/dL)	0 (0%)	1 (2%)	1 (2%)
Hospitalised for management of cardiac or pulmonary disease	11 (24%)	6 (14%)	8 (18%)
Time from infusion to surgery, median (IQR), h	40.9 (26.0–44.7)	40.9 (28.2–44.2)	41.3 (24.8–44.8)
Time on cardiopulmonary bypass, median (IQR), h	1.8 (1.3–2.3)	1.7 (1.5–2.4)	1.6 (1.3–2.3)
Surgery Type			
CABG alone	24 (52%)	23 (55%)	22 (50%)
Valve alone	11 (24%)	13 (31%)	8 (18%)
CABG + Valve	11 (24%)	6 (14%)	14 (32%)

Data are n (%) unless otherwise specified. Percentages are rounded. The underlined values represent the number of patients recruited in each of the countries by treatment group. CABG = coronary artery bypass graft. EuroSCORE = European system for cardiac operative risk evaluation. NYHA=New York Heart Association.

Table 1: **Baseline characteristics (intent-to-treat population).**

low-dose RBT-1 group, and 1.00 in the placebo group (Table 2, Supplementary Figure S1). Both high-dose and low-dose RBT-1 were associated with an increased preconditioning biomarker response compared with placebo (high-dose vs. placebo; GLSM ratio, 3.58; 95% CI, 2.91–4.41; p < 0.0001; and low-dose vs. placebo; GLSM ratio, 2.62; 95% CI, 2.11–3.24; p < 0.0001).

Secondary outcomes of AKI incidence and sustained reduction in urine output were numerically lower with both doses of RBT-1 compared with placebo but the differences were not significant (Table 3). The composite of renal tubular injury biomarkers occurred with similar frequency in the RBT-1 and placebo groups, and these biomarkers did not correlate with the maximum change in serum creatinine (data not shown). The primary composite outcome results in the MITT population were consistent with the results in the ITT population.

RBT-1 was generally well tolerated by patients. The primary drug-related AE was photosensitivity, a known reaction to the SnPP component of RBT-1 (Table 4). Photosensitivity was dose-dependent, occurring in 12 of 46 patients (26%) treated with high-dose RBT-1 and in 6 of 45 patients (13%) treated with low-dose RBT-1 in the safety population. In general, photosensitivity reactions were transient and mild to moderate in intensity. The median time of onset of photosensitivity was 2.0 days in the high-dose RBT-1 group and 2.5 days in the low-dose

	High-dose (n = 46)	Low-dose (n = 42)	Placebo (n = 44)	High-dose vs. placebo		Low-dose vs. placebo	
				GLSM Ratio (95% CI)	p value	GLSM Ratio (95% CI)	p value
Biomarker response, GLSM[a]	3.60	2.63	1.00	3.58[b] (2.91–4.41)	<0.0001	2.62[b] (2.11–3.24)	<0.0001

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

Table 2: **Primary outcome (intent-to-treat population).**

	High-dose (n = 41)	Low-dose (n = 39)	Placebo (n = 41)	High-dose vs. placebo, risk ratio (95% CI)	Low-dose vs. placebo, risk ratio (95% CI)
Acute kidney injury	7 (17%)	7 (18%)	8 (20%)	0.88 (0.35–2.19)	0.92 (0.37–2.30)
Sustained reduction in urine output	2 (5%)	2 (5%)	4 (10%)	0.50 (0.10–2.58)	0.53 (0.10–2.71)
Tubular injury biomarker response, GLSM[a]	7.9	10.8	6.1	1.29[b] (0.71–2.35)	1.78[b] (0.96–3.30)
Biomarker response, GLSM[a]	3.60	2.62	1.00	3.61[b] (2.91–4.47)	2.62[b] (2.11–3.27)

Data are n (%) unless otherwise specified. Percentages are rounded. GLSM = geometric least squares mean. [a]GLSM of the ratio of max post-op value over baseline. [b]GLSM ratio represents GLSM in the active treatment group over GLSM in the placebo group.

Table 3: **Secondary outcomes (modified intent-to-treat population).**

RBT-1 group; median time to resolution was 7.0 days in the high-dose RBT-1 group and 3.5 days in the low-dose RBT-1 group. All photosensitivity reactions resolved within 93 days in the high-dose RBT-1 group and within 28 days in the low-dose RBT-1 group. Three photosensitivity reactions in the high-dose RBT-1 group resulted in delayed surgery. Other AEs of general interest are also provided (Table 4).

Post-operative complications included 2 (5%) deaths in the high-dose RBT-1 group, 1 (3%) death in the low-dose RBT-1 group, and 3 (7%) deaths in the placebo group (Supplementary Table S6). Dialysis for AKI was needed in 1 (2%) patient in the placebo group but none in either RBT-1 group. The number of patients with MAKE was relatively low, and no statistical differences between groups were observed. Post-operative atrial fibrillation and hypervolemia were numerically lower in both RBT-1 groups compared with placebo, but the differences were not significant. The mean time on ventilator was 1.2 days, 1.7 days, and 2.4 days in the high-dose RBT-1, low-dose RBT-1, and placebo groups, respectively (Supplementary Figure S2 and Supplementary Table S6). The mean time in ICU was 3.3 days in both RBT-1 groups and 6.0 days in the placebo group. The mean time in hospital was 9.1 days, 8.3 days, and 10.0 days in the high-dose RBT-1, low-dose RBT-1, and placebo groups, respectively. Finally, 2 (5%) patients each in both RBT-1 groups were readmitted to the hospital at 30-days post-discharge for a cardiopulmonary diagnosis compared with 7 patients (18%) in the placebo group. Through 60 days and 90 days post-discharge, the cardiopulmonary readmission rate remained the same in both RBT-1 groups with 2 (5%) patients each readmitted compared with an increase to 8 (21%) patients in the placebo group. All-cause readmissions showed similar results.

Given the suggested multi-organ benefit of RBT-1, we explored the effects of RBT-1 in a post-hoc composite analysis (win ratio) wherein clinical outcomes were assessed in rank order of severity (death > AKI requiring dialysis > ICU days >30-day cardiopulmonary readmission) in the MITT population. The win ratio was 1.39 (95% CI, 0.80–2.42) in patients treated with high-dose RBT-1 and 2.26 (95% CI, 1.23–4.15) with low-dose RBT-1 compared with placebo (Supplementary Table S7).

In a post-hoc analysis of myocardial injury using troponin I, the rise in troponin I after cardiac surgery (GLSM of the ratio between 1-day post-operative values and preoperative baseline values) was numerically lower in the high-dose RBT-1 group compared with placebo but the difference was not significant (GLSM ratio, 0.71; 95% CI, 0.32–1.58). However, the rise in postoperative troponin I was reduced in the low-dose RBT-1 group compared with placebo (GLSM ratio, 0.37; 95% CI, 0.17–0.82) (Supplementary Figure S3). The analysis population, derived from the MITT population, excluded patients who had undergone mitral valve repair or replacement, ablation, or septal myectomy due to the expected large increase in troponin I levels following these major surgeries.

Discussion

This study of RBT-1 met its primary outcome, demonstrating a statistically significant increase in the levels of cytoprotective proteins (plasma HO-1, IL-10, and ferritin), which are surrogate measures for RBT-1-mediated activation of a preconditioning response. The RBT-1 biomarker response was consistent with the phase 1 b study.[23] The overall incidence of AKI was low and differences in AKI-related outcomes were not

	High-dose (N = 46)	Low-dose (N = 45)	Placebo (N = 44)	High-dose vs. placebo, risk difference (95% CI)	Low-dose vs. placebo, risk difference (95% CI)
Primary drug-related adverse event					
Photosensitivity reaction	12 (26%)	6 (13%)	0 (0%)	26.1 (14.2–41.1)	13.3 (3.8–27.0)
Deaths					
Death	2 (4%)	1 (2%)	3 (7%)	−2.5 (−15.1 to 8.9)	−4.6 (−16.5 to 5.8)
Adverse events					
Participants with at least 1 adverse event	44 (96%)	40 (89%)	40 (91%)	4.7 (−6.9 to 17.8)	−2.0 (−16.2 to 12.0)
Hypotension	14 (30%)	12 (27%)	12 (27%)	3.2 (−16.0 to 22.0)	−0.6 (−19.6 to 18.3)
Nausea	14 (30%)	9 (20%)	9 (21%)	10.0 (−8.5 to 28.0)	−0.5 (−18.3 to 16.8)
Pleural effusion	12 (26%)	11 (24%)	11 (25%)	1.1 (−17.4 to 19.4)	−0.6 (−18.9 to 18.3)
Atrial fibrillation	10 (22%)	12 (27%)	17 (39%)	−16.9 (−35.9 to 2.4)	−12.0 (−31.3 to 7.9)
Atelectasis	11 (24%)	11 (24%)	10 (23%)	1.2 (−17.3 to 19.4)	1.7 (−16.5 to 20.5)
Procedural pain	9 (20%)	9 (20%)	11 (25%)	−5.4 (−23.7 to 12.9)	−5.0 (−22.9 to 12.9)
Anaemia	6 (13%)	8 (18%)	11 (25%)	−12.0 (−28.9 to 4.7)	−7.2 (−24.9 to 10.4)
Urine output decreased	6 (13%)	4 (9%)	4 (9%)	4.0 (−10.7 to 18.5)	−0.2 (−14.0 to 14.0)
Hyperglycaemia	5 (11%)	5 (11%)	5 (11%)	−0.5 (−15.1 to 13.7)	−0.3 (−15.0 to 14.1)
Hypervolaemia	5 (11%)	4 (9%)	10 (23%)	−11.9 (−28.1 to 4.1)	−13.8 (−30.1 to 1.8)
Constipation	5 (11%)	4 (9%)	4 (9%)	1.8 (−12.6 to 15.7)	−0.2 (−14.0 to 14.0)
Urinary tract infection	5 (11%)	0 (0%)	1 (2%)	8.6 (−2.6 to 21.6)	−2.3 (−12.1 to 5.8)
Acute kidney injury	4 (9%)	8 (18%)	6 (14%)	−4.9 (−19.5 to 9.1)	4.1 (−11.8 to 20.5)
Incision site pain	4 (9%)	6 (13%)	2 (5%)	4.2 (−8.4 to 17.3)	8.8 (−3.9 to 22.7)
Leukocytosis	4 (9%)	3 (7%)	6 (14%)	−4.9 (−19.5 to 9.1)	−7.0 (−21.5 to 6.7)
Oedema peripheral	3 (7%)	6 (13%)	2 (5%)	2.0 (−9.8 to 13.9)	8.8 (−3.9 to 22.7)
Generalised oedema	3 (7%)	3 (7%)	5 (11%)	−4.8 (−19.4 to 8.5)	−4.7 (−18.7 to 8.5)
Dyspnoea	3 (7%)	2 (4%)	4 (9%)	−2.6 (−16.0 to 10.5)	−4.6 (−18.3 to 7.3)
Pneumothorax	3 (7%)	2 (4%)	2 (5%)	2.0 (−9.8 to 13.9)	−0.1 (−11.7 to 11.7)
Subcutaneous emphysema	3 (7%)	2 (4%)	0 (0%)	6.5 (−2.0 to 17.9)	4.4 (−4.0 to 15.2)
Diarrhoea	3 (7%)	1 (2%)	3 (7%)	−0.3 (−12.9 to 12.1)	−4.6 (−16.5 to 5.8)
Pulmonary oedema	3 (7%)	1 (2%)	2 (5%)	2.0 (−9.8 to 13.9)	−2.3 (−14.0 to 7.8)
Atrial flutter	3 (7%)	1 (2%)	1 (2%)	4.2 (−6.3 to 15.8)	−0.1 (−10.0 to 9.8)
Non-cardiac chest pain	3 (7%)	0 (0%)	1 (2%)	4.2 (−6.3 to 15.8)	−2.3 (−12.1 to 5.8)
Insomnia	2 (4%)	5 (11%)	5 (11%)	−7.0 (−20.8 to 5.1)	−0.3 (−15.0 to 14.1)
Blood loss anaemia	2 (4%)	4 (9%)	4 (9%)	−4.7 (−17.8 to 6.9)	−0.2 (−14.0 to 14.0)
Thrombocytopenia	2 (4%)	4 (9%)	3 (7%)	−2.5 (−15.1 to 8.9)	2.1 (−11.1 to 15.4)
Delirium	2 (4%)	3 (7%)	3 (7%)	−2.5 (−15.1 to 8.9)	−0.2 (−12.9 to 12.4)
Cardiomegaly	2 (4%)	3 (7%)	2 (5%)	−0.2 (−11.7 to 10.7)	2.1 (−9.6 to 14.1)
Oedema	2 (4%)	2 (4%)	4 (9%)	−4.7 (−17.8 to 6.9)	−4.6 (−18.3 to 7.3)
Chest pain	2 (4%)	1 (2%)	3 (7%)	−2.5 (−15.1 to 8.9)	−4.6 (−16.5 to 5.8)
Cardiogenic shock	1 (2%)	4 (9%)	1 (2%)	−0.1 (−10.7 to 9.6)	6.6 (−4.4 to 19.1)
Agitation	1 (2%)	3 (7%)	1 (2%)	−0.1 (−10.7 to 9.6)	4.4 (−6.2 to 16.2)
Breath sounds abnormal	1 (2%)	3 (7%)	1 (2%)	−0.1 (−10.7 to 9.6)	4.4 (−6.2 to 16.2)
Pneumonia	1 (2%)	2 (4%)	3 (7%)	−4.6 (−17.3 to 5.8)	−2.4 (−14.7 to 9.5)
Pain	1 (2%)	1 (2%)	5 (11%)	−9.2 (−22.6 to 1.9)	−9.1 (−22.7 to 2.1)
Respiratory failure	1 (2%)	1 (2%)	3 (7%)	−4.6 (−17.3 to 5.8)	−4.6 (−16.5 to 5.8)
Abdominal distension	1 (2%)	0 (0%)	3 (7%)	−4.6 (−17.3 to 5.8)	−6.8 (−18.7 to 1.6)
Cellulitis	1 (2%)	0 (0%)	3 (7%)	−4.6 (−17.3 to 5.8)	−6.8 (−18.7 to 1.6)
Hallucination	1 (2%)	0 (0%)	3 (7%)	−4.6 (−17.3 to 5.8)	−6.8 (−18.7 to 1.6)
Hypoxia	0 (0%)	3 (7%)	2 (5%)	−4.5 (−15.5 to 4.1)	2.1 (−9.6 to 14.1)
Vomiting	0 (0%)	2 (4%)	3 (7%)	−6.8 (−18.7 to 1.9)	−2.4 (−14.7 to 9.5)
Epistaxis	0 (0%)	0 (0%)	3 (7%)	−6.8 (−18.7 to 1.9)	−6.8 (−18.7 to 1.6)

Data are n (%) unless otherwise specified. Percentages are rounded.

Table 4: **Safety events (safety population).**

significant in this population. Despite the relatively small sample size of this study, we observed a reduction in adverse post-operative outcomes, suggesting that RBT-1 may improve recovery after cardiac surgery.

Cardiac surgery, especially with cardiopulmonary bypass, induces systemic inflammation, which can lead to multi-organ dysfunction, impacting clinical outcomes.[30] Importantly, inflammation and oxidative stress exist in a feed-forward loop, magnifying the response of each pathway. The detrimental effect of these cell-damaging mediators can be seen in the phenomenon of "organ crosstalk," wherein damage in one organ leads to damage in another.[31–33]

The benefits observed with RBT-1 are likely related to mitigation of these adverse effects by activating anti-inflammatory and antioxidant pathways prior to surgery, thereby resulting in direct and indirect beneficial effects in various organs. For example, the RBT-1-mediated anti-inflammatory response may prevent extravasation of fluid into tissues due to capillary leakage, thus reducing the need for fluid (volume) replacement and ultimately fluid overload as observed by the reduction in hypervolemia in RBT-1-treated patients. The broad organ protective benefits of RBT-1 may result in an improvement in clinical outcomes as manifested by reduced time on ventilator, time in ICU, need for vasopressors, new-onset atrial fibrillation, and fluid overload in the short-term and a decrease in cardiopulmonary hospital readmissions in the long-term. To further assess this hypothesis, we explored the effects of RBT-1 in a post-hoc analysis using a win ratio based on a composite of clinical outcomes assessed in rank order of severity. This assessment, which consisted of death, AKI requiring dialysis, ICU days, and 30-day cardiopulmonary readmission, suggested clinical improvement in response to RBT-1, which will be confirmed in an upcoming phase 3 study.

The safety profile of RBT-1 showed that it was well tolerated, with the primary drug-related AE being photosensitivity, which was dose-related and time-limited. The SnPP component (a metalloporphyrin) of RBT-1 is likely the cause of photosensitivity as metalloporphyrins are light responsive and may lead to a sunburn in patients exposed to the sun, especially if sun exposure is prolonged or sunscreen is not used. The low-dose of RBT-1 (45 mg SnPP/240 mg FeS) is planned for the definitive phase 3 trial due to comparable efficacy and fewer photosensitivity reactions compared with high-dose RBT-1.

This study has some limitations. As a phase 2 trial, the aim was to investigate whether RBT-1 administered before surgery would elicit a preconditioning response in patients undergoing CABG and/or heart valve surgery and was not powered (i.e., relatively small sample size) to demonstrate statistically significant reductions in clinical outcomes; a larger phase 3 trial is needed to demonstrate such effects. This study was conducted during the COVID-19 pandemic, which may have impacted the LOS in ICU; however, to minimise variability in standard of care, patients were randomised at the centre level. Although composite outcomes showing statistically significant improvement were evaluated in a post-hoc analysis, a consistent trend of improvement with RBT-1 treatment was observed. One (0.7%) patient had incomplete serum creatinine values required for the MAKE outcome at Day 60 and 90 due to COVID-19 that prevented the patient from returning to the hospital for lab collection. However, we imputed laboratory values for this patient. Given the exploratory nature of the trial, the type I error rate was not controlled using bias adjustment methods. Use of other measures of myocardial injury (e.g., troponin T or creatine kinase myocardial band [CK-MB]) and ventricular function (i.e., echocardiogram) could provide important information in future trials.

In conclusion, this phase 2 study of RBT-1 met its primary outcome, demonstrating a statistically significant increase in the levels of cytoprotective proteins (plasma HO-1, IL-10, and ferritin), which are surrogate measures for RBT-1-mediated activation of a preconditioning response. Given the positive trends in clinical outcomes and adequate safety profile, a phase 3 study of RBT-1 is planned, wherein the primary outcome will be a hierarchical composite of clinical outcomes.

Contributors

SR and BS acquired funding for the research and CW, SS, JR, SR, BS curated the research data and conducted the statistical analysis. AL, GMC, SR, BS drafted the manuscript. AL (academic) and BS (commercial) accessed and verified the underlying data and had final responsibility for the decision to submit for publication. All authors reviewed, provided comments on the manuscript, and gave approval of the version to be published.

Data sharing statement

Deidentified data collected for the study, including aggregated participant data and related documents (e.g., protocol, statistical analysis plan), will be made available for an indefinite period beginning 24 months following publication of the Article. Requests for data access will be reviewed by the corresponding author upon receipt of a reasonable request. Requests should be directed to lamya@mcmaster.ca. To facilitate the approval process and gain access, data requestors will need to provide a draft of a data access agreement, which will undergo evaluation to determine its suitability and compliance with our data sharing policies.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102364.

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