STATISTICAL ANALYSIS PLAN

Protocol number: REN-004

A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Effect of RBT-1 on Preconditioning Response Biomarkers in Subjects Undergoing Coronary Artery Bypass Graft (CABG) and/or Cardiac Valve Surgery

The START Study

Date of Final Statistical Analysis Plan:	21 September 2021 version 1.0 19 April 2022, version 2.0 16 November 2022, version 3.0

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Revision History

Version	Date	Author	Summary of Changes
1.0	21 September 2021	Chao Wang	First signed off version
2.0	12 April 2022	Chao Wang	Globally, baseline is changed to Visit 1a. Section 7.2 a description for handling missing central lab tests or aberrant test results is provided. Section 7.3 is updated to be more specific for adaptation rule. Section 7.5 is updated for the primary and secondary endpoints derivation. Section 7.6 is added to include additional parameters of interest.
3.0	01 November 2022	Chao Wang	See Section 2.3.

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LIST OF ABBREVIATIONS

AE	Adverse event
AKI	Acute kidney injury
ANCOVA	Analysis of Covariance
AUC	Area under the curve
Avg	Average
CABG	Coronary artery bypass graft
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel χ^2 test
CSR	Clinical study report
CysC	Cystatin C
eCRF	Electronic case report form
Exp	Exponential
FeS	Iron sucrose
GM	Geometric mean
GLSM	Geometric least squares mean
HO-1	Heme oxygenase-1
ICU	Intensive Care Unit
IL-10	Interleukin-10
IV	Intravenous
KDIGO	Kidney disease improving global outcomes
KIM-1	Kidney injury molecule-1
LLOQ	Lower limit of quantification
Log	Natural logarithm (base e)
LSM	Least Squares Mean
MAKE	Major adverse kidney events
MAKE30	Major Adverse Kidney Events through Day 30 post-cardiac surgery
MAKE90	Major Adverse Kidney Events through Day 90 post-cardiac surgery
MINP	Method of inverse normal p-values
MITT	Modified intent to treat
MMRM	Mixed model for repeated measures
NGAL	Neutrophil gelatinase-associated lipocalin
PostOp	Post cardiac surgery
PreOp	Immediately prior to the cardiac surgery
RBT-1	Stannous protoporphyrin and iron sucrose
SAE	Serious adverse event
SAP	Statistical analysis plan
SnPP	Stannous protoporphyrin
TEAE	Treatment-emergent adverse event

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to present the statistical methodology that will be used for the interim and final analyses of Renibus Therapeutics, Inc. protocol REN-004. This plan also provides a description of the tables, figures, and listings that will be included in the final statistical report. It is based on the protocol version 5 dated 25 August 2022 and on the annotated electronic case report form (eCRF). In case of differences in terms of descriptions or explanations between the SAP and the clinical protocol, the SAP will supersede the protocol. Any deviation to this SAP would be reported in the clinical study report (CSR).

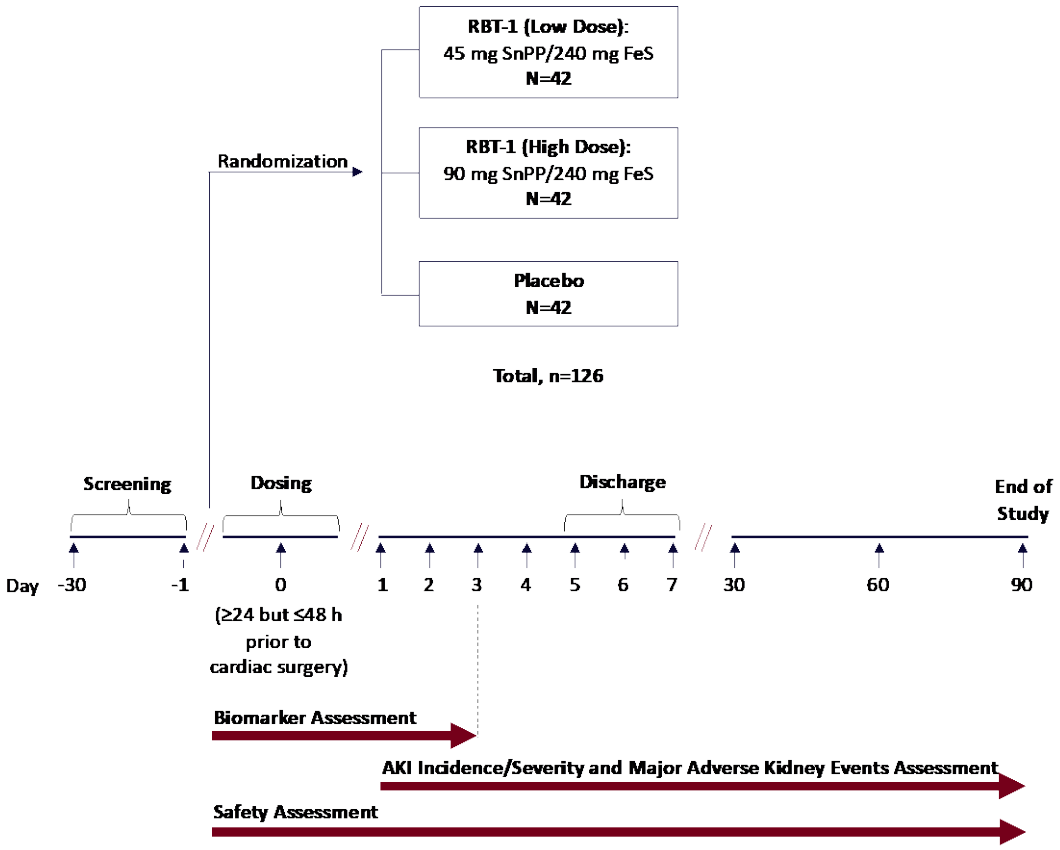
2 STUDY DESCRIPTION

2.1 Study Design

This is a Phase 2, multicenter, double-blind, randomized, placebo-controlled study to evaluate the effect of RBT-1 on preconditioning response biomarkers in subjects who are at risk for acute kidney injury (AKI) following cardiac surgery. Eligible subjects will be randomized to receive a single dose of low dose RBT-1 (45 mg SnPP/240 mg FeS), high dose RBT-1 (90 mg SnPP/240 mg FeS), or placebo (normal saline) via intravenous (IV) infusion over a 120-minute period ≥24 but ≤48 hours prior to scheduled cardiac surgery.

All subjects will be assessed through Day 90 post-cardiac surgery. Subjects will be evaluated at Screening, 48 and/or 24 hours prior to surgery depending on the time of dosing, on Day 1 (day of surgery), and daily through Day 7 or Discharge if earlier, as well as on Days 30, 60, and 90, as described in the Event Schedule (see Appendix 1). Assessments include biomarkers of preconditioning response and tubular injury, urine output, incidence and severity of AKI, serum creatinine, days on ventilator, days in intensive care unit, hospital length of stay, readmission rate, and safety (physical examination, clinical laboratory assessment, vital signs, concomitant medications, and adverse events). Evaluations for major adverse kidney events (MAKE) (death, need for dialysis, and persistent decrease in kidney function) and safety will be performed through Day 90, as described in the Event Schedule (see Appendix 1).

The duration of the study will be approximately 90 days per subject. A schematic of the study design is presented below:



AKI = acute kidney injury, FeS = iron sucrose, h = hour, SnPP = stannous protoporphyrin

2.2 Study Objectives

The overall objective is to evaluate the effect of RBT-1 on preconditioning response biomarkers in subjects undergoing CABG and/or cardiac valve surgery.

The primary objective is to evaluate the efficacy of RBT-1 in generating a preconditioning response as measured by a composite of plasma biomarkers (plasma heme oxygenase-1 [HO-1], ferritin, and interleukin-10 [IL-10]) from Baseline (pre-dose) through Day 1 PreOp.

The secondary objectives are to evaluate the efficacy of RBT-1 on the following:

- Change in renal tubular injury biomarkers post-cardiac surgery through Day 3
- Reduction in urine output (documented adverse event [AE] of sustained reduction in urine output, oliguria, or anuria) post-cardiac surgery through Day 5
- Incidence of AKI (defined as a ≥1.5X baseline, i.e., a 50% increase from baseline in serum creatinine; documented AE of sustained reduction in urine output, oliguria, or anuria; or initiation of dialysis) post-cardiac surgery through Day 5

The exploratory objectives are to evaluate the following:

- Severity of AKI post-cardiac surgery through Day 7
- Mean increase in serum creatinine post-cardiac surgery through Day 7 or until Discharge if prior to Day 7
- Occurrence of MAKE – death, need for dialysis, and persistent renal dysfunction (≥25% decrease in estimated glomerular filtration rate [eGFR]) – post-cardiac surgery through Day 30 (MAKE30) and Day 90 (MAKE90) post-cardiac surgery
- Proportion of subjects experiencing MAKE30
- Proportion of subjects experiencing MAKE90
- Days on ventilator
- Days in intensive care unit (ICU)
- Hospital length of stay
- Readmission rate
- Changes in biomarkers of RBT-1 activity and/or kidney function

2.3 Changes from v2.0 to v3.0 Statistical Analysis Plan

See APPENDIX B for detail.

3 ANALYSIS POPULATIONS

The populations of analysis will be confirmed by the Sponsor prior to unblinding.

3.1 Intent-To-Treat (ITT) Population

The ITT population will consist of all randomized subjects who were eligible for the study, received study drug, and had biomarker assessments performed at baseline (Visit 1a) and prior to surgery (Visit 1b and/or Day 1 PreOp). Subjects in the ITT population will be analyzed as randomized.

3.2 Modified Intent-To-Treat (MITT) Population

The MITT population will consist of all randomized subjects who were eligible for the study, received study drug, underwent CABG and/or cardiac valve surgery without delay, and were evaluated through the end of index surgery hospitalization. Subjects in the MITT population will be analyzed as randomized.

3.3 Safety Population

The safety population will consist of all subjects who received any amount of study drug. Subjects in the Safety population will be analyzed as per actual treatment received.

4 DEFINITIONS

4.1 Baseline

Baseline is defined as the last value collected prior to the start of the study drug administration, unless specified otherwise. This usually is the value collected at Visit 1a Predose for vital signs, serum chemistry, hematology, and blood and urine biomarkers. If missing, then the value collected at unscheduled visit or Visit 0, whichever is available and more recent to study drug administration, will be used.

4.2 Study Day

To be consistent with the protocol definition, Study Day 1 is the day of the cardiac surgery. Study Days 2, 3, 4, 5, 6 7, 30, 60 and 90 are the nominal days following Study Day 1.

4.3 Start/Stop Day

For adverse events or prior/concomitant medications, unless specified otherwise, the start day and the stop day are calculated from the date of the study drug administration.

Event day = event date – study drug administration date + 1 if the event is on/after study drug date, or

Event day = event date – study drug administration date if the event is before study drug date.

5 EFFICACY ENDPOINTS

5.1 Primary Efficacy Endpoint

The primary efficacy composite endpoint is defined as the geometric mean of the ratios of the maximum PreOp value (Visit 1b or Day 1 PreOp) over Baseline (Visit 1a) for the 3 preconditioning biomarkers,

$$Exp\left\{\frac{1}{3}\cdot\left[Log\left(\frac{\text{max PreOp HO-1}}{\text{Baseline HO-1}}\right)+Log\left(\frac{\text{max PreOp Ferritin}}{\text{Baseline Ferritin}}\right)+Log\left(\frac{\text{max PreOp IL-10}}{\text{Baseline IL-10}}\right)\right]\right\}.$$

For sensitivity analysis, this composite endpoint will also be defined as the geometric mean of the ratios of average of Day 1 PostOp through Day 3 over baseline for the 3 preconditioning biomarkers {HO-1, Ferritin, and IL-10}, where Avg (average) is calculated as the area under the biomarker-time curve (AUC) divided by the duration in the AUC calculation (AUC/D), and

$$AUC=\left\{\sum_{i=2}^{n}(v_i+v_{(i-1)})(t_i-t_{(i-1)})\right\}/2,$$
$$D=t_n-t_1$$

v_1 and v_n are the first (Visit 1b or Day 1 for subjects dosed 36 to 48 hours or 24 to <36 hours prior to surgery, respectively) and last (Study Day 3) biomarker values after study drug administration, t_i is the date and time of the i^{th} biomarker test.

Baseline for this composite endpoint is calculated as

(Baseline HO-1 * Baseline ferritin * Baseline IL-10)1/3.

Because an increase in plasma biomarkers is beneficial and because the ratios are calculated as the follow-up value over the baseline value, a value >1 for the primary efficacy endpoint would indicate benefit.

5.2 Secondary Efficacy Endpoints

5.2.1 Maximum PostOp over Baseline in Renal Tubular Injury Biomarkers

The secondary efficacy composite endpoint is defined as the geometric mean of the ratios of the maximum PostOp value (Day 1, 1 hour post cardiac surgery through Day 3) over Baseline (Visit 1a) for the 3 tubular injury biomarkers,

$$\text{Exp}\Big[\ 1/3 * \Big(Log\left(\frac{\text{max(KIM-1 PostOp through Day 3)}}{\text{Baseline KIM-1}}\right) + Log\left(\frac{\text{max(CysC PostOp through Day 3)}}{\text{Baseline CysC}}\right) + Log\left(\frac{\text{max(NGAL PostOp through Day 3)}}{\text{Baseline NGAL}}\right)\Big)\ \Big].$$

Baseline for this composite endpoint is calculated as

$$(\text{Baseline KIM-1} * \text{Baseline CysC} * \text{Baseline NGAL})^{1/3}.$$

Because a lack of increase in renal tubular injury biomarkers is considered beneficial and because the ratios are calculated as the follow-up value over the baseline value, a value >1 would indicate an increased risk.

This endpoint is expected to capture the kidney injury manifested by any of the 3 biomarkers at any time in the 3 days following the surgery.

5.2.2 Reduction in Urine Output

The reduction in urine output (documented AE of sustained reduction in urine output, oliguria, or anuria) post-cardiac surgery through Day 5 will be evaluated by the site and captured as an AE on the AE log eCRF.

5.2.3 Incidence of AKI

The incidence of AKI post-cardiac surgery through Day 5 will be defined as:

- An absolute increase from baseline to ≥1.5 x Baseline at any time; or
- A documented AE of sustained reduction in urine output, oliguria, or anuria; or
- Initiation of dialysis

5.3 Exploratory Efficacy Endpoints

5.3.1 Severity of AKI

Maximum severity of AKI post-cardiac surgery through Day 7 will be a categorical variable. It is defined as the maximum severity over Days 2 through 7 for subject with AKI incidence PostOp through Day 7 (replacing Day 5 with Day 7 in Section 5.2.3) as follows:

Stage 1 if $Creat_{Di}$- $Creat_{BL}$ >= 0.3 mg/dL, or

$1.5*Creat_{BL} <= Creat_{Di} < 2*Creat_{BL}$ (i=2 to 7)

Stage 2 if $2*Creat_{BL} <= Creat_{Di} < 3*Creat_{BL}$ (i=2 to 7)

Stage 3 if $Creat_{Di}$- $Creat_{BL}$ >= 4 mg/dL, or
$3*Creat_{BL} <= Creat_{Di}$ (i=2 to 7), or
need for dialysis and date of dialysis < date of surgery +6

where $Creat_{BL}$ is creatinine at baseline (Day 1 PreOp), $Creat_{Di}$ is creatinine on Day D_i (i.e., Days 2, …, 7).

5.3.2 Mean increase from Baseline in Serum Creatinine

Mean increase in serum creatinine will be computed as the average of the post-baseline serum creatinine through Day 7 or Discharge, whichever is earlier, minus baseline serum creatinine. Baseline is defined as the serum creatinine collected at Visit 1a time point.

5.3.3 Occurrence of MAKE

Endpoints related to MAKE are as follows:

- Proportion of subjects experiencing either MAKE30, MAKE60, or MAKE90
- Proportion of subjects experiencing MAKE30
- Proportion of subjects experiencing MAKE60
- Proportion of subjects experiencing MAKE90

MAKE30 is defined for subjects with AKI incidence PostOp through Day 5 as follows

- Death (of all cause) and date of death < date of surgery + 30, or
- Need for dialysis and date of dialysis < date of surgery + 30, or
- $(eGFRD_{30} - eGFR_{BL})/eGFR_{BL} <= -0.25$ PostOp through Day 30

MAKE60 is defined for subjects with AKI incidence PostOp through Day 5 as follows

- Death (of all cause) and date of death < date of surgery + 60, or
- Need for dialysis and date of dialysis < date of surgery + 60, or
- $(eGFRD_{60} - eGFR_{BL})/eGFR_{BL} <= -0.25$ PostOp through Day 60

MAKE90 is defined for subjects with AKI incidence PostOp through Day 5 as follows

- Death (of all cause) and date of death < date of surgery + 90, or
- Need for dialysis and date of dialysis < date of surgery + 90, or
- $eGFRD_{90} - eGFR_{BL})/eGFR_{BL} <= -0.25$ PostOp through Day 90

where $eGFR_{BL}$ is eGFR at baseline (Day 1 PreOp), $eGFR_{30}$, $eGFR_{60}$, and $eGFR_{90}$ are eGFR on Days 30, 60, and 90, respectively. Note, eGFR (mL/min/1.73m^2) is calculated using 2009 CKD-EPI equation:

$$141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if African American]}.$$

5.3.4 Hospitalization Parameters

Parameters related to hospitalization are as follows:

- Number of days on ventilator
- Number of days in intensive care unit (ICU)
- Hospital length of stay in days
- Readmission rate, defined as the proportion of subjects who are readmitted to a hospital following discharge from the initial hospitalization for CABG and/or cardiac valve surgery

5.3.5 Change in Biomarkers of RBT-1 Activity and/or Kidney Function

The change in each exploratory biomarker will be computed for the intervals from baseline (Visit 1A) to Day 1 (Visit 2), Day 2 (Visit 3), and Day 3 (Visit 4).

6 SAFETY PARAMETERS

Safety will be assessed through adverse events (AEs) and serious adverse events (SAEs), clinical laboratory parameters, physical examination, and vital signs.

6.1 Adverse Events

Adverse Event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

All AEs will be recorded on the designated study eCRF for each subject beginning with the administration of investigational product and ending with the date of the end of study treatment follow-up (Day 90). AEs will be followed by the Investigator until event resolution, the subject is lost to follow-up, or the AE is otherwise explained or not considered clinically significant by the Investigator. AEs not resolved by Day 90 will be considered ongoing.

When reporting AEs, the Investigator will assess the relationship or association of study drug in causing or contributing to the adverse event as well as the intensity of the adverse event.

Treatment-emergent AEs (TEAEs) will be defined as any AE where the AE start date is on or after the infusion start date. AEs related to study treatment will be defined as any AE where the relationship to study treatment is considered as “possible” or “related”.

6.2 Serious Adverse Events

An adverse event is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Other medically important event

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.3 Select Adverse Events of Interest

Following is a list of adverse events of interest by MedDRA preferred term (tentative):

- Atrial fibrillation
- Delirium
- Vasoplegia
- Bleeding
- Myocardial infraction
- Stroke
- Heart failure
- AKI (combined AKI, ARF, AE report of sustained urine reduction)
- Death

Additionally, photosensitivity AEs will be identified.

6.4 Laboratory Parameters

Screening laboratory samples will be processed at a local laboratory. All other laboratory samples will be processed at a central laboratory. For subjects who will be administered study drug on the same day of Screening, blood and urine samples will need to be collected for central laboratory analysis in accordance with Visit 1a.

Serum chemistry and hematology will be measured at Screening (Visit 0), Visit 1a, Day 1 PreOp (Visit 2), and on Days 2 to 7 (or discharge, whichever is earlier; Visits 3-8), Day 30 (Visit 9), Day 60 (Visit 10), and Day 90 (Visit 11). Serum CysC will only be measured at Visit 1a and on Days 30 (Visit 9) and 90 (Visit 11).

Serum chemistry parameters include total protein, albumin, bicarbonate, blood urea nitrogen (BUN), serum creatinine, total bilirubin, alkaline phosphatase, glucose, sodium, potassium, phosphate, calcium, magnesium, gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and CysC.

Hematology parameters include RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, MPV, RDW and WBC.

Blood and urinary biomarkers will be collected at Visit 1a, 1b, 2 (PreOp, 1h PostOp, 12h PostOp), 3 (Day 2) and 4 (Day 3).

Blood biomarkers include preconditioning response biomarkers (plasma HO-1, ferritin, and IL-10) and other biomarkers of RBT-1 activity and kidney function.

Urinary biomarkers include tubular injury biomarkers (KIM-1, CysC, and NGAL) and other biomarkers of RBT-1 activity and kidney function, which include but are not limited to urine albumin to creatinine ratio (UACR), urine protein to creatinine ratio (UPCR), beta-2-microglobulin, osteopontin, calbindin, clusterin, and VEGF.

Blood and urine samples may be collected by remote phlebotomy, such as through a mobile phlebotomist or other blood collection center, for a visit conducted virtually on Day 7, 30, 60, or 90.

6.5 Other Safety Parameters

Physical examinations should be performed at Screening, prior to dosing, prior to cardiac surgery on Day 1, Day 7, Day 30, and Day 90. Symptom-directed physical examinations may be performed on Days 2 – 6. Symptom-directed physical examinations may also be performed on Days 7, 30, and 90 if those visits are conducted virtually.

Weight and body mass index will be collected at Screening and on Day 90.

Vital signs (blood pressure, pulse rate, body temperature) will be collected throughout the study at Screening (Visit 0), Visit 1a, Day 1 PreOp (Visit 2), and on Days 2 to 90 (Visit 3 to 11). During hospitalization, vital signs will be recorded once per day.

At each post-cardiac surgery visit, the Investigator/study staff will record whether the subject is in the ICU, on a ventilator, has been discharged from the hospital, or readmitted to the hospital.

7 STATISTICAL METHODOLOGY

7.1 Determination of Sample Size

There will be three treatment groups; the two active (high dose [HD] 90/240 and low dose [LD] 45/240) groups will be compared to the control group. Using gatekeeping procedure for multiple comparisons and assuming the primary endpoint log composite score derived from this study is comparable to the score derived from the REN-003 and REN-001A studies (HD: mean ± SD 1.30±0.56, LD: 1.07±0.52, and placebo: 0.19±0.19), a sample size of 10 subjects per group will provide >80% power for the between group comparisons with two-sided α=0.05 significance level.

Using the REN-003 Study “FDA Safety Summary-1 Updated Feb2020.docx” non-surgical healthy volunteer and CKD patient data mixture, the secondary endpoint log composite score is estimated as 0.41 ± 0.51. Thus, with the sample size of 10, 20, and 30 subjects per group, the study will have 40%, 69%, and 86% power, respectively, to detect a between active group and placebo group difference in the mean log composite score of 0.4, or a between group ratio of 1.5 in the composite score.

7.2 General Statistical Considerations

Continuous variables will be summarized overall and by treatment group using descriptive statistics (e.g., N, mean, median, standard deviation [SD], Q1, Q3, minimum and maximum), while categorical variables will be summarized with number and proportion of subjects for each category.

In addition to the data summary and between group comparison, all data will be presented in the data listings with subject ID, treatment group, and other pertinent information.

For serum creatinine and eGFR, missing or aberrant central lab test results will be replaced by the local lab test results if available, or if not available, by linear interpolation by the two data points before and after the missing data point (not applicable for Day 7, Day 30, 60, and 90 tests). If Visit 1a is missing, and the corresponding local lab is not available, it will be imputed with the screening local lab result. Day 7 (Visit 8) lab test is collected on the nominal Day 7. If patients are discharged early, their discharge values from Days 4, 5, or 6 will be reported as Day 7 values. If Day 7 is missing, and the corresponding local lab result is not available, it will be imputed with the last value collected Day 3 through Day 6. All imputations will be documented and signed off prior to the database lock for analysis. Biomarker values below the limit of quantification (LLOQ) will be replaced by the LLOQ value divided by 2. Biomarker values above the limit of quantification (ULOQ) will be replaced by the ULOQ value.

Unless specified otherwise, all between group comparisons and confidence intervals will use 2-sided a=0.05 significance level.

Statistical analyses will be performed using SAS version 9.4 or higher.

7.3 Multiple Comparison and Two-Stage Design

The gatekeeping procedure will be applied to protect the overall type-I error rate due to the multi-dose active treatments vs the placebo comparisons. Specifically, the HD group will be compared to the placebo group first for the primary efficacy endpoint with a=0.05. If p-value is <0.05, then the LD group will be compared to placebo for the primary efficacy endpoint also with a=0.05. If the HD group is not statistically significant in the first comparison, the LD group will automatically be considered not significant for the primary efficacy endpoint.

The study will potentially be carried out in two stages. The first stage (Stage 1) will enroll approximately 20 subjects per treatment group for a total of 60 subjects. After these first 60 subjects have completed the efficacy assessments through Day 30, an interim analysis will be conducted to compare the primary efficacy endpoints between each active dose group against placebo.

- 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.

- If a significant difference (p≤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
- If one of the active dose groups is dropped, the remaining active dose and placebo groups will continue into Stage 2 for another 30 subjects per treatment group.
- The Stage 2 population may be adapted based on the AKI risk factor distribution in the interim analysis population, which includes but is not limited to the following:
    - Estimated glomerular filtration rate (eGFR) ≥20 and <30 mL/min/1.73m^2 **
    - Estimated glomerular filtration rate (eGFR) ≥30 and <60 mL/min/1.73m^2
    - Age ≥65 years
    - Combined valve and coronary surgery
    - Previous cardiac surgery with sternotomy
    - Documented New York Heart Association Class III or IV within 1 year prior to surgery
    - Left ventricular ejection fraction ≤35%
    - Congestive heart failure
    - Diabetes mellitus requiring insulin
    - Type 2 diabetes mellitus with albuminuria (urine albumin >300 mg/g of creatinine as documented in medical history)
    - Current inpatient status for management of cardiac or pulmonary disease
    - Preoperative anemia (hemoglobin <10 g/dL upon Screening)

  ** Condition eGFR ≥20 and <30 is taken as 2 counts. All other conditions listed above are taken as 1 count.

Note that in this study, the composite preconditioning biomarkers are being measured for the first time in cardiac surgery patients treated with the study medication. Because of the multi-dimensional data and lack of prior knowledge, it is not possible to plan all potential adaptations upfront. Therefore, the above adaptation rule will only serve as a guidance. As such, no type-I error will be adjusted for the potential 2-stage design and analysis.

If enrollment for Stage 2 is adapted based on AKI risk factors, subjects in Stage 2 will be analyzed separately from subjects in Stage 1. If so, Stage 1 and Stage 2 can be viewed as two separate studies. Hence, the Stage 2 analysis will independently use the gatekeeping procedure with the same 2-sided a=0.05. If there are enough high-risk subjects in Stage 1 (eg, N≥5/group), the high-risk Stage 1 subjects may be pooled with Stage 2 subjects as a secondary analysis.

7.4 Study Subjects

7.4.1 Subject Disposition and Analysis Population

Number of screened subjects, randomized subjects, study drug-treated subjects, and subjects receiving surgery will be provided overall and by treatment group. In addition, the number of randomized subjects completing the study and the reasons for discontinuation will be summarized overall and by treatment group.

Information on subject disposition will also be listed.

7.4.2 Protocol Deviations

Major protocol deviations will be summarized overall and by treatment group for the randomized population. A listing will also be provided.

7.4.3 Study Populations

The number of subjects in each study population will be summarized overall and by treatment group.

7.4.4 Demographic and Baseline Characteristics

Demographic data and baseline characteristics, including a general medical history, will be summarized overall and by treatment group for the ITT and MITT populations.

AKI risk factors will be summarized by number of subjects meeting each risk factor, number of subjects meeting categorical and cumulative number of risk factors (eg, 0, 1-2, ≥1, ≥2, and ≥3).

7.4.5 Study Drug Administration and Surgery

Time of study drug administration before surgery, duration of infusion, duration of surgery, and time on pump will be summarized descriptively with mean and median by treatment group. Subjects with infusion interruption and subjects with infusion discontinuation will be summarized with number (n) and percent (%) of subjects by treatment group.

7.4.6 Prior and Concomitant Medication

All medications taken by subjects from the time of Screening through Day 90 will be recorded. Medications will be coded for the therapeutic class and preferred term using the WHO Drug Dictionary (WHODD September 2021).

Subject incidence of prior medications, defined as medications taken prior to the study drug administration, will be summarized with number and % of subjects by therapeutic class and preferred term, overall and by treatment group, for the Safety and MITT population. Subject incidence of concomitant medications, defined as medications taken on/after the day of study drug administration, will be summarized similarly.

7.5 Efficacy Analysis

Primary endpoint will be analysed using both the ITT and MITT populations. All other efficacy endpoints will be analyzed using the MITT population.

Surgery type and time on pump may be used as covariates in ANCOVA or MMRM, or as stratification factor in Cochran-Mantel-Haenszel (CMH) χ^2 test. When used as stratification factor, time on pump will be trichotomized by the approximate tertile (≤90, >90 to 120, >120 minutes) of the distribution in the MITT population. Other variables (eg, AKI risk factor and investigator site) may also be considered as covariates or stratification factors. The decision for including/excluding these variables as covariates or stratification factors will be based on the blinded review prior to any unblinded analysis.

7.5.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint (geometric mean of the ratios of maximum PreOp over baseline in preconditioning biomarkers, Section 5.1) will be summarized using descriptive statistics (N, mean, median, standard deviation, minimum, and maximum) in the log scale and presented after the anti-log (exponential) transformation for each group separately.

An analysis of covariance (ANCOVA) model will be applied to the log-transformed primary efficacy endpoint. The model will include treatment group as main effect, and surgery type and time on-pump as covariates. Least squares mean (LSM) and the 95% confidence interval (CI) will be calculated for each treatment group and for the between active treatment and placebo difference. The LSM (95% CI) will be anti-log transformed and presented as the geometric LSM (GLSM) and 95% CI for each treatment group, and GLSM ratio (and 95% CIs) for each active treatment over placebo.

A sensitivity analysis will be carried out by the Cochran-Mantel-Haenszel (CMH) χ^2 test for the row mean score difference between active treatment and placebo stratified by the surgery type and time on pump. A modified ridit score will be used in the calculation of the CMH test statistic. As a supplementary analysis for the primary endpoint, each component of the composite endpoint

- $\frac{\text{max PreOp HO-1}}{\text{Baseline HO-1}}$
- $\frac{\text{max PreOp ferritin}}{\text{Baseline ferritin}}$
- $\frac{\text{max PreOp IL-10}}{\text{Baseline IL-10}}$

will be analyzed in the same way as for the primary efficacy endpoint.

7.5.2 Secondary Efficacy Endpoint Analysis

7.5.2.1 Max PostOp over baseline in the composite of renal tubular injury biomarkers

The secondary endpoint (geometric mean of the ratios of maximum PostOp over baseline in renal tubular injury biomarkers, Section 5.2.1) will be summarized and analyzed similarly to the primary endpoint.

Likewise, each component of the composite endpoint

- $\frac{\text{max KIM-1 PostOp through Day 3)}}{\text{Baseline KIM-1}}$
- $\frac{\text{max(CysC PostOp through Day 3)}}{\text{Baseline CysC}}$
- $\frac{\text{max(NGAL over PostOp through Day 3)}}{\text{Baseline NGAL}}$

will be analyzed similarly to the composite endpoint.

A sensitivity analysis will be conducted for the maximum of the ratios of maximum PostOp over baseline in renal tubular injury biomarkers (see Section 5.2.1).

7.5.2.2 Reduction in Urine Output

The proportion of subjects with reduction in urine output (ie, subjects with a documented AE of sustained reduction in urine output, oliguria, or anuria) through Day 5 will be presented for each treatment group. Reduction in urine output (yes/no) will also be analyzed using the Fisher's exact test for the comparison between each active treatment group and the placebo group.

7.5.2.3 Incidence of AKI

Incidence of AKI through Day 5 defined in Section 5.2.3 will be presented using proportions and analyzed using the Fisher's exact test as described above for reduction in urine output.

As a sensitivity analysis, subject incidence of ≥0.3 mg/dL and ≥0.5 mg/dL increase from baseline over 2 consecutive measurements at least 12 hours apart in serum creatinine from post-cardiac surgery through Day 5 will be analyzed similarly.

7.5.3 Exploratory Analysis

7.5.3.1 Severity of AKI

Maximum severity of AKI through Day 7 will be summarized by presenting the proportion of subjects in each severity stage in each treatment group. CMH test for the row mean score difference will be used for the between active treatment and placebo difference stratified by the surgery type and time on pump. A modified ridit score will be used in the CMH test.

7.5.3.2 Mean increase from baseline in serum creatinine

Mean changes and % mean changes from baseline (defined as Visit 1a) to the mean of creatinine PostOp through Day 7 (or discharge if earlier) will be summarized by treatment group. The between active treatment and placebo difference in mean change and % mean change will be analyzed using ANCOVA with treatment as main effect and baseline as a covariate. LSM difference and the associated 95% CI will be presented.

Additionally, the CMH test stratified by the baseline creatinine in approximately tertile (≤0.9, >0.9 to 1.2, >1.2 mg/dL) will be carried out as a sensitivity analysis.

Analysis of change and % change from baseline to each post-dose visit through Day 90 (i.e., Days 1, 2, 3, 4, 5, 6, 7, 30, 60, and 90) will be analyzed using the mixed effects model for repeated measures (MMRM), which includes treatment, visit, and treatment-by-visit interaction as factors, baseline as a covariate, and subject as repeated measure unit. The LSM and 95% CI will be presented for each treatment group at each time point. In the computation, the variance-covariance matrix will be assumed AR(1) structure and the denominator degrees-of-freedom will be estimated using the improved Kenward-Rodger method. LSM and 95% for the between active dose and placebo group difference will also be presented at each time point.

7.5.3.3 Mean reduction from Baseline in estimated glomerular filtration rate (eGFR)

Mean change and % mean change from baseline (defined as Visit 1a) in eGFR (mL/min/1.73m^2) will be summarized and analyzed similarly to that for the serum creatinine.

7.5.3.4 Occurrence of MAKE

Proportions of subjects with (1) either MAKE30, MAKE60, or MAKE90, (2) MAKE30, (3) MAKE60, and (4) MAKE90 will be calculated and analyzed using the Fisher's exact test as described for the reduction in urine output.

7.5.3.5 Hospitalization parameters

Number of days on ventilator, number of days in intensive care unit and length of hospital stay will be summarized by treatment group with descriptive statistics of mean, median, and SD. Appropriate statistical tests will be applied for the between treatment comparison. Exploratory analysis may be carried out using the Kaplan-Meier survival method. The between treatment difference will be tested using the log-rank test. Proportion of subjects who are re-admitted to the hospital after the initial hospital stay for the cardiac surgery will be calculated for Days 30, 60, and 90 and analyzed using the Fisher's exact test.

Additionally, the association between hospital parameters and the primary efficacy endpoint (as well as HO-1, IL-10, and ferritin) will be explored graphically by X-Y scatter plot and curve fitting for each treatment group.

As an exploratory analysis, numbers of days on ventilator, in ICU, and in the initial hospitalization, and hospital readmission rate will be summarized by the below subgroup.

- Type of surgery (CABG vs valve vs CABG and valve combined)
- Inpatient vs outpatient for the initial hospitalization
- CKD vs non-CKD
- Number of risk factors at baseline (≤2 vs >2, and 0, 1-2, ≥3)

7.6 Safety Analysis

The safety analyses described in this section will be conducted on the safety population.

7.6.1 Adverse Events

AEs will be coded by system organ class (SOC) and preferred term according to the MedDRA dictionary (version 24.1).

TEAEs will be summarized for subject incidence rate. An overall summary of TEAEs that includes the total number of TEAEs reported, the number and proportion of subjects experiencing at least one TEAE, at least one severe TEAE, at least one treatment-related TEAE, at least one serious TEAE, at least one TEAE leading to study discontinuation, and at least one TEAE resulting in death will be displayed by treatment group.

The number and proportion of subjects experiencing a TEAE will also be presented by SOC and PT by treatment group.

Overall and by PT incidence rate will be summarized for subjects with TEAE of interest (Section 6.3) for each treatment group. Overall subject incidence rate for photosensitivity TEAEs will also be summarized for each treatment group.

A listing of all AEs will be provided. Separate listings will be created for all serious AEs, AEs leading to study discontinuation, and deaths.

7.6.2 Laboratory Parameters

Screening laboratory samples for chemistry, hematology and urinalysis will be processed at a local laboratory. All other laboratory samples will be processed at a central laboratory. For chemistry and hematology parameters, results at each visit will be summarized by treatment group. In addition, shift tables will also be presented within treatment groups.

All laboratory results will be listed.

7.6.3 Other Safety Parameters

Weight, body mass index, and vital signs (blood pressure, pulse rate, body temperature) at each scheduled visit and change from baseline at each visit will be summarized by treatment group. Physical examination results will be listed. Details of hospitalization(s) will be listed.

8 SUMMARY TABLES, FIGURES, AND LISTINGS

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9 APPENDICES

APPENDIX A – Schedule of Visits

Visit	Visit 0 (Screening)†	Visit 1a	Visit 1b††	Visit 2		Visit 3	Visit 4	Visits 5-7	Visit 8*	Visit 9*	Visit 10*	Visit 11*/ Final Visit
Procedure / Time point	**Within 30 Days Prior to Visit 1**	**≥24 h but ≤48 h Prior to Surgery**	**24 h (± 4 h) Prior to Surgery**	**D1 Pre-Op**	**D1 Post-Op**	**D2**	**D3**	**D4, 5, 6 (If Hospitalized)**	**D7** (± 3 days)	**D30** (± 3 days)	**D60** (± 3 days)	**D90** (± 3 days)
Informed Consent Form	X											
Patient Eligibility (Inclusion/Exclusion Criteria)	X	X										
Demographics	X											
Medical History	X											
Prior/Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X		X		X [1]	X [1]	X [1]	X	X		X
Weight and BMI	X											X
Vital Signs	X	X		X		X	X	X	X	X	X	X
Serum Chemistry [2]	X [3]	X		X		X	X	X	X	X	X	X
Hematology [4]	X	X		X		X	X	X	X	X	X	X
Urinalysis [5]	X									X		X
Urine Output [6]					X	X	X					
Blood Biomarkers [7]		X	X	X [8]		X	X					
Urinary Biomarkers [9]		X	X	X [8]		X	X					
Urine Pregnancy Test [10]	X									X		
Study Drug Infusion [11]		X										
Adverse Events [12]		X	X	X	X	X	X	X	X	X	X	X

BMI = body mass index; D = Day; h = hour; PostOp = post-operatively; PreOp = pre-operatively

† Screening labs will be analyzed at a local laboratory; for subjects who will be administered study drug on the same day of Screening, blood and urine samples will need to be collected for central laboratory analysis in accordance with Visit 1a; physical examinations and routine labs (serum chemistry, hematology, urinalysis) performed as part of standard of care within 1 month of dosing administration (Visit 1a) can be used for Screening assessments.

†† Visit 1b will be performed in subjects who receive study drug within 36 to 48 hours prior to surgery.

* Visits 8-11 (Days 7, 30, 60, and 90) may be conducted remotely as virtual visits if in-person visits are not possible; if virtual visits are conducted: 1) blood and urine samples may be collected by remote phlebotomy, such as through a mobile phlebotomist or other blood collection center and 2) physical examinations can be symptom-directed.

1 Physical examination can be symptom-directed on Days 2-6.
2 Serum chemistry parameters include total protein, albumin, bicarbonate, blood urea nitrogen, serum creatinine, total bilirubin, alkaline phosphatase, glucose, sodium, potassium, phosphate, calcium, magnesium, gamma-glutamyl transferase, alanine aminotransferase, aspartate aminotransferase, and cystatin C.
3 Serum ferritin is also to be assessed at Screening if not already included in local laboratory chemistry panel.
4 Hematology parameters include red blood cell count [RBC], hemoglobin, hematocrit, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], platelets, mean platelet volume [MPV], red cell distribution width [RDW], white blood cell count [WBC], and WBC differential (including neutrophils [absolute and percentage], lymphocytes [absolute and percentage], monocytes [absolute and percentage], eosinophils [absolute and percentage], and basophils [absolute and percentage]).
5 Urinalysis parameters include glucose, ketones, leukocytes, nitrite, blood, pH, protein, specific gravity, and reflex microscopic.
6 Urine output will be measured through Day 3.
7 Blood biomarkers include preconditioning response biomarkers (plasma heme oxygenase-1 [HO-1], ferritin, and interleukin-10 [IL-10]) and other biomarkers of RBT-1 activity and kidney function.
8 Blood and urinary biomarkers will be collected within 4 hours prior to cardiac surgery.
9 Urinary biomarkers include tubular injury biomarkers (kidney injury molecule-1 [KIM-1], cystatin C, and neutrophil gelatinase-associated lipocalin [NGAL]), and other biomarkers of RBT-1 activity and kidney function.
10 A pregnancy test will be performed in female subjects of childbearing potential.
11 RBT-1 and placebo will be administered via intravenous infusion over a 120-minute period.
12 Adverse events assessment will include photosensitivity assessment.

APPENDIX B – Change from Version 2.0 SAP to this Version 3.0 SAP

Section 2.2 The secondary objectives are to evaluate the efficacy of RBT-1 on the following:

v2.0

- Reduction in urine output (documented oliguria of <0.5 mL/kg/hour, not due to urinary tract obstruction or hypotension) for more than 6 hours post-cardiac surgery through Day 3
- Incidence of AKI (defined using the modified Kidney Disease Improving Global Outcomes [KDIGO] criteria) post-cardiac surgery through Day 5

v3.0

- Reduction in urine output (documented adverse event [AE] of sustained reduction in urine output, oliguria, or anuria) post-cardiac surgery through Day 5
- Incidence of AKI (defined as a ≥1.5X baseline, i.e., a 50% increase from baseline in serum creatinine; documented AE of sustained reduction in urine output, oliguria, or anuria; or initiation of dialysis) post-cardiac surgery through Day 5

Section 3.1 Modified Intent-to-Treat (MITT) Population

v2.0

- None

v3.0

- The ITT population will consist of all randomized subjects who were eligible for the study, received study drug, and had biomarker assessments performed at baseline (Visit 1a) and prior to surgery (Visit 1b and/or Day 1 PreOp). Subjects in the ITT population will be analyzed as randomized.

Section 3.2 Modified Intent-to-Treat (MITT) Population

v2.0

- The MITT population will consist of all randomized subjects who were eligible for the study, received study drug, underwent CABG and/or cardiac valve surgery without delay, and have at least one post baseline primary efficacy assessment. Subjects in the MITT population will be analyzed as randomized.

v3.0

- The MITT population will consist of all randomized subjects who were eligible for the study, received study drug, underwent CABG and/or cardiac valve surgery without delay, and were evaluated through the end of index surgery hospitalization. Subjects in the MITT population will be analyzed as randomized.

Section 3.3 Per Protocol Population

v2.0

The per-protocol population will consist of subjects from the MITT population who had primary efficacy assessments through Day 3 and had no major protocol violations. Subjects with major protocol deviations will be identified using the eCRF Form Protocol Deviation ([“Any protocol deviation” = “Yes”] and [“Deviation Impact” is not reported as “Minor”]). Subjects in the Per Protocol population will be analyzed as treated.

v3.0

This section is removed.

Section 5.2.2 Reduction in Urine Output

v2.0

- The reduction in urine output (documented oliguria of <0.5 mL/kg/hour, not due to urinary tract obstruction or hypotension) for 6 or more consecutive hourly assessments post-cardiac surgery through Day 3 will be evaluated by the site and captured as a (Yes/No) binary variable on the daily eCRF.

v3.0

- The reduction in urine output (documented AE of sustained reduction in urine output, oliguria, or anuria) post-cardiac surgery through Day 5 will be evaluated by the site and captured as an AE on the AE log eCRF.

Section 5.2.3 Incidence of AKI

The incidence of AKI post-cardiac surgery through Day 5 will be defined as:

v2.0

- An absolute increase from baseline in serum creatinine by 0.5 mg/dL, which is present over 2 consecutive laboratory measurements at least 12 hours apart; or
- An increase in serum creatinine ≥1.5 x Baseline at any time

This secondary efficacy endpoint will be a binary variable and will be derived as presented in Appendix 2.

v3.0

- An absolute increase from baseline to ≥1.5 x Baseline at any time; or
- A documented AE of sustained reduction in urine output, oliguria, or anuria; or
- Initiation of dialysis

Section 5.3.1 Severity of AKI

v2.0

Maximum severity of AKI post-cardiac surgery through Day 7 will be a categorical variable (stage 1, stage 2, and stage 3) and will be as presented in Appendix 2.

v3.0

Maximum severity of AKI post-cardiac surgery through Day 7 will be a categorical variable. It is defined as the maximum severity over Days 2 through 7 for subject with AKI incidence PostOp through Day 7 (replacing Day 5 with Day 7 in Section 5.2.3) as follows:

Stage 1 if $Creat_{Di}$- $Creat_{BL}$ >= 0.3 mg/dL, or
$1.5*Creat_{BL}$ <= $Creat_{Di}$ < $2*Creat_{BL}$ (i=2 to 7)
Stage 2 if $2*Creat_{BL}$ <= $Creat_{Di}$ < $3*Creat_{BL}$ (i=2 to 7)
Stage 3 if $Creat_{Di}$- $Creat_{BL}$ >= 4 mg/dL, or
$3*Creat_{BL}$ <= $Creat_{Di}$ (i=2 to 7), or
need for dialysis and date of dialysis < date of surgery + 7

where $Creat_{BL}$ is creatinine at baseline (Day 1 PreOp), $Creat_{Di}$ is creatinine on Day D_i (i.e., Days 2, …, 7).

Section 5.3.3 Occurrence of MAKE

v2.0

Endpoints related to MAKE are as follows:

- Proportion of subjects experiencing either MAKE30 or MAKE90 post-cardiac surgery
- Proportion of subjects experiencing MAKE30
- Proportion of subjects experiencing MAKE90

These efficacy endpoints will be binary variables and will be derived as presented in Appendix 3.

v3.0

Endpoints related to MAKE are as follows:

- Proportion of subjects experiencing either MAKE30, MAKE60, or MAKE90
- Proportion of subjects experiencing MAKE30
- Proportion of subjects experiencing MAKE60
- Proportion of subjects experiencing MAKE90

MAKE30 is defined for subjects with AKI incidence PostOp through Day 5 as follows

- Death (of all cause) and date of death < date of surgery + 30, or
- Need for dialysis and date of dialysis < date of surgery + 30, or
- $(eGFRD_{30} - eGFR_{BL})/eGFR_{BL}$ <= -0.25 PostOp through Day 30

MAKE60 is defined for subjects with AKI incidence PostOp through Day 5 as follows

- Death (of all cause) and date of death < date of surgery + 60, or
- Need for dialysis and date of dialysis < date of surgery + 60, or
- ($eGFRD_{60}$ - $eGFR_{BL}$)/$eGFR_{BL}$ <= -0.25 PostOp through Day 30

MAKE90 is defined for subjects with AKI incidence PostOp through Day 5 as follows

- Death (of all cause) and date of death < date of surgery + 90, or
- Need for dialysis and date of dialysis < date of surgery + 90, or
- $eGFRD_{90}$ - $eGFR_{BL}$)/$eGFR_{BL}$ <= -0.25 PostOp through Day 30

where $eGFR_{BL}$ is eGFR at baseline (Day 1 PreOp), $eGFR_{30}$, $eGFR_{60}$, and $eGFR_{90}$ are eGFR on Days 30, 60, and 90, respectively. Note, eGFR (mL/min/1.73m^2) is calculated using 2009 CKD-EPI equation:

$$141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if African American]}.$$

Section 6.3 Select Adverse Events of Interest

v2.0

This section is inserted in v3.0.

v3.0

Following is a list of adverse events of interest by MedDRA preferred term (tentative):

- Atrial fibrillation
- Delirium
- Vasoplegia
- Bleeding
- Myocardial infraction
- Stroke
- Heart failure
- AKI (combined AKI, ARF, AE report of sustained urine reduction)
- Death

Section 7.4.4 Demographic and Baseline Characteristics

v2.0

- AKI risk factors will be summarized by number of subjects meeting each risk factor, and number of subjects meeting cumulative number of risk factors (eg, ≥1, ≥2).

v3.0

- AKI risk factors will be summarized by number of subjects meeting each risk factor, number of subjects meeting categorical and cumulative number of risk factors (eg, 0, 1-2, ≥1, ≥2, and ≥3).

Additionally, photosensitivity AEs will be identified.

Section 7.5 Efficacy Analysis

v2.0

All efficacy analyses will be conducted on the MITT population. The primary efficacy endpoint analysis will be repeated for the PP population.

When used as stratification factor, time on pump will be trichotomized by the tertile of the distribution in the MITT population.

v3.0

Primary endpoint will be analysed using both the ITT and MITT populations. All other efficacy endpoints will be analyzed using the MITT population.

When used as stratification factor, time on pump will be trichotomized by the approximate tertile (≤90, >90 to 120, >120 minutes) of the distribution in the MITT population.

Section 7.5.2.2 Reduction in Urine Output

v2.0

- The proportion of subjects with reduction in urine output for ≥6 hours through Day 3 will be presented for each treatment group.

v3.0

- The proportion of subjects with reduction in urine output (ie, subjects with a documented AE of sustained reduction in urine output, oliguria, or anuria; or initiation of dialysis) through Day 5 will be presented for each treatment group.

Section 7.5.2.3 Incidence of AKI

v2.0

- As a sensitivity analysis, subject incidence of ≥0.3 mg/dL increase from baseline … will be analyzed similarly.

v3.0

- As a sensitivity analysis, subject incidence of ≥0.3 mg/dL and ≥0.5 mg/dL increase from baseline … will be analyzed similarly.

Section 7.5.3.2 Mean increase from baseline in serum creatinine

v2.0

- Additionally, the CMH test stratified by the baseline creatinine in tertile will be carried out as a sensitivity analysis.

- Analysis of change and % change from baseline to each PostOp visit through Day 7 (i.e., Days 1, 2, 3, 4, 5, 6, and 7) will be analyzed using …

v3.0

- Additionally, the CMH test stratified by the baseline creatinine in approximately tertile (≤0.9, >0.9 to 1.2, >1.2 mg/dL) will be carried out as a sensitivity analysis.
- Analysis of change and % change from baseline to each post-dose visit through Day 7 (i.e., Days 1, 2, 3, 4, 5, 6, and 7) will be analyzed using …

Section 7.5.3.4 Occurrence of MAKE

v2.0

Proportions of subjects with (1) either MAKE30 or MAKE90, (2) MAKE30, and (3) MAKE90 will be calculated and analyzed using the Fisher's exact test as described for the reduction in urine output. This summary will be presented for subjects who develop AKI incidence (see Table 2.2 in Appendix 2) during hospitalization, subjects who do not develop AKI incidence during hospitalization, and all subjects.

v3.0

Proportions of subjects with (1) either MAKE30, MAKE60, or MAKE90, (2) MAKE30, (3) MAKE60, and (4) MAKE90 will be calculated and analyzed using the Fisher's exact test as described for the reduction in urine output.

Section 7.5.3.5 Hospital parameters

v2.0

Number of days on ventilator, number of days in intensive care unit and length of hospital stay will be summarized by treatment group. Proportion of subjects who are re-admitted to the hospital after the initial hospital stay for the cardiac surgery will be calculated.

v3.0

Number of days on ventilator, number of days in intensive care unit and length of hospital stay will be summarized by treatment group with descriptive statistics of mean, median, and SD. Appropriate statistical tests will be applied for the between treatment comparison. Additional analysis may be carried out using the Kaplan-Meier survival method. The between treatment difference will be tested using the log-rank test. Proportion of subjects who are re-admitted to the hospital after the initial hospital stay for the cardiac surgery will be calculated for Days 30, 60, and 90 and analyzed using the Fisher's exact test.

Additionally, the association between hospital parameters and the primary efficacy endpoint (as well as HO-1, IL-10, and ferritin) will be explored graphically by X-Y scatter plot and curve fitting for each treatment group.

As an exploratory analysis, numbers of days on ventilator, in ICU, and in the initial hospitalization, and hospital readmission rate will be summarized by the below subgroup.

- Type of surgery (CABG vs valve vs CABG and valve combined)
- Inpatient vs outpatient for the initial hospitalization
- CKD vs non-CKD
- Number of risk factors at baseline (≤2 vs >2, and 0, 1-2, ≥3)
- Baseline EUROSCORE tertile
- Baseline STS score tertile

Also as an exploratory analysis, composite score constructed by the weighted sum of the ventilator days, ICU days, and initial hospital days will be derived. The weight will be derived based on the resource utilization for each of these 3 parameters.

Section 7.5.3.6 Change in Biomarkers of RBT-1 Activity and/or Kidney function

V2.0

Change and % change from baseline (Visit 1a) to the Day 1 – 7 average biomarker values will be summarized by treatment group. The active treatment and placebo difference will be analyzed similar to that for the mean change in creatinine using the MMRM method.

V3.0

This section is removed.

Section 7.6. Additional Parameters for Analysis

v2.0

Variables of interest:

1. Single incidence of ≥50% increase from baseline in serum creatinine.
2. Single incidence of ≥50% increase from baseline in serum creatinine AND sustained serum creatinine increase through Day 30, 60, and/or 90
3. Persistent AKI, defined as serum creatinine increase from baseline for ≥ 48 hours and ≥ 72 hours by
    - ≥ 0.3 mg/dL
    - ≥ 0.5 mg/dL
    - ≥ 50%
4. Persistent AKI during the initial hospitalization, as defined in #3 above, **AND** sustained serum creatinine increase through Day 30, 60, and/or 90
5. Persistent AKI during the initial hospitalization, as defined in #3 above, **AND** eGFR decrease of ≥25%, ≥30%, and ≥50% on Day 30, 60, and/or 90
6. eGFR decrease by
    - ≥ 25%
    - ≥ 30%

- ≥ 50%

from baseline during initial hospitalization for

- ≥ 48 hours
- ≥ 72 hours

7. eGFR decrease as defined in #6 above **AND** sustained through Day 30, 60, and/or 90
8. Worsening proteinuria at Day 30 and/or 90 compared with baseline
9. Worsening albuminuria at Day 30 and/or 90 compared with baseline
10. MAKE outcomes and the association with the parameters defined in #1-#9 above, including percent of subjects meeting each criterion who have MAKE
11. Days on ventilator and the association with the parameters defined in #1-#9 above
12. Days in intensive care unit (ICU) and the association with the parameters defined in #1-#9 above
13. Hospital length of stay and the association with the parameters defined in #1-#9 above
14. Readmission rate and the association with the parameters defined in #1-#9 above

v3.0

This section is completely removed.

Section 7.6.1 Adverse Events

v2.0

This paragraph is newly added to v3.0.

v3.0

Overall and by PT incidence rate will be summarized for subjects with TEAE of interest (Section 6.3) for each treatment group. Overall subject incidence rate for photosensitivity TEAEs will also be summarized for each treatment group.

Appendix 1 Schedule of Visits

v3.0

- V2.0 Schedules for “D1 1h Post-Op” is replaced with “D1 Post-Op” and v2.0 “D1 12h Post-Op” is removed.

Footnote

v2.0

6 Urine output will be measured until Discharge.
8 Blood and urinary biomarkers will be collected within 1 hour prior to cardiac surgery.

v3.0

6 Urine output will be measured through Day 3.
8 Blood and urinary biomarkers will be collected within 4 hours prior to cardiac surgery.

Appendix 2 Derivation of occurrence and severity of AKI

v2.0

The data that will be used to derive occurrence and severity of AKI post-cardiac surgery through Day 7 is schematically presented in the table below.

Table 2.1 - Format of the data to derive occurrence of AKI

Visit	**$Creat_{Di}$ (mg/dL)**	**Change from Baseline (Visit 1A)**	**Change from BL >= 0.5 mg/dL**	**$Creat_{Di}$ >= 1.5*$Creat_{BL}$**	**Severity of AKI**	**(GFR_{Di} – GFR_{BL})/GFR_{BL} <= -0.25**
Baseline (Visit 1A) (before dosing)	$Creat_{BL}$	0	N/A	N/A	N/A	N/A
D1 PreOp (after dosing but prior surgery)	$Creat_{preop}$	$Creat_{preop}$- $Creat_{BL}$	no need to calculate	no need to calculate	no need to calculate	no need to calculate
D2	$Creat_{D2}$	$Creat_{D2}$- $Creat_{BL}$	Yes or No	Yes or No	NA, stage 1, stage 2 or stage 3	no need to calculate
D3	$Creat_{D3}$	$Creat_{D3}$- $Creat_{BL}$	Yes or No	Yes or No	NA, stage 1, stage 2 or stage 3	no need to calculate
D4	$Creat_{D4}$	$Creat_{D4}$- $Creat_{BL}$	Yes or No	Yes or No	NA, stage 1, stage 2 or stage 3	no need to calculate
D5	$Creat_{D5}$	$Creat_{D5}$- $Creat_{BL}$	Yes or No	Yes or No	NA, stage 1, stage 2 or stage 3	no need to calculate
D6	$Creat_{D6}$	$Creat_{D6}$- $Creat_{BL}$	Yes or No	Yes or No	NA, stage 1, stage 2 or stage 3	no need to calculate
D7	$Creat_{D7}$	$Creat_{D7}$- $Creat_{BL}$	Yes or No	Yes or No	NA, stage 1, stage 2 or stage 3	no need to calculate
D30	$Creat_{D30}$	no need to calculate	no need to calculate	no need to calculate	no need to calculate	Yes or No
D60	$Creat_{D60}$	no need to calculate	no need to calculate	no need to calculate	no need to calculate	Yes or No
D90	$Creat_{D90}$	no need to calculate	no need to calculate	no need to calculate	no need to calculate	Yes or No

In the table above, eGFR (mL/min/1.73m^2) is calculated using 2009 CKD-EPI equation:

$$141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if African American]}$$

where: $S_{cr}$is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1

If a patient is considered to have an AKI incidence, then the severity of AKI, defined as stage, is derived as follows:

Stage 1 if $Creat_{Di}$- $Creat_{BL}$ >= 0.3 mg/dL OR 1.5*$Creat_{BL}$ <= $Creat_{Di}$ < 2*$Creat_{BL}$ (i=2 to 7)
Stage 2 if 2*$Creat_{BL}$ <= $Creat_{Di}$ < 3*$Creat_{BL}$ (i=2 to 7)
Stage 3 if $Creat_{Di}$- $Creat_{BL}$ >= 4 mg/dL OR 3*$Creat_{BL}$ <= $Creat_{Di}$ (i=2 to 7) OR need for dialysis and date of dialysis < date of surgery + 7

Occurrence and severity of AKI will be derived as presented in the tables below.

Table 2.2 – Derivation of occurrence of AKI (subject level)

Incidence of AKI post-cardiac surgery through Day 7 (subject level)	Derivation
Yes	If there are two consecutive "Yes" for *Change from baseline (visit 1a) >= 0.5 mg/dL* from D2 to D5 OR If there is one "Yes" for *$Creat_{Di}$ >= 1.5*$Creat_{BL}$* from D2 to D5
No	Otherwise

Table 2.3 – Derivation of severity of AKI (subject level)

Severity of AKI post-cardiac surgery through Day 7 (subject level)	Derivation
Stage 1	If Incidence of AKI post-cardiac surgery through Day 7 ='Yes' AND Maximum severity of AKI from D2 to D7 = 'Stage 1'
Stage 2	If Incidence of AKI post-cardiac surgery through Day 7 ='Yes' AND Maximum severity of AKI from D2 to D7 = 'Stage 2'
Stage 3	If Incidence of AKI post-cardiac surgery through Day 7 ='Yes' AND Maximum severity of AKI from D2 to D7 = 'Stage 3' OR If Incidence of AKI post-cardiac surgery through Day 7 ='Yes' AND Need for dialysis and the date of dialysis < date of surgery + 7

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This appendix is completely removed.

Appendix 3 – Derivation of occurrence of MAKE

v2.0

Table 3.1 - Derivation of severity of MAKE 30 (subject level)

Occurrence of MAKE30	Derivation
Yes	If death (all-cause mortality) and date of death < date of surgery + 30 OR if need for dialysis and the date of dialysis < date of surgery + 30 OR If subject has incidence of AKI post-cardiac surgery through Day 5 AND ($eGFR_{D30}$ - $eGFR_{BL}$)/$eGFR_{BL}$ <= -0.25
No	Otherwise

Table 3.2 - Derivation of severity of MAKE 90 (subject level)

Occurrence of MAKE90	Derivation
Yes	If death (all-cause mortality) and date of death < data of surgery + 90 OR if need for dialysis and the date of dialysis < date of surgery + 90 OR If subject has incidence of AKI post-cardiac surgery through Day 5 AND ($eGFR_{Di}$ - $eGFR_{BL}$)/$eGFR_{BL}$ <= -0.25 on D30, D60 and D90
No	Otherwise

v3.0

This appendix is completely removed.

Section 8 Summary Tables, Figures, and Listings

v2.0

Below tables, listings, and figures are removed from v3.0 as a result of the SAP update.

Table 14.2-3.1 Subject Incidence of Reduction in Urine Output Post Surgery Through Day 3 (per the Urine Output eCRF) - MITT Population
Table 14.2-4.1 Subject Incidence and Max Severity of Acute Kidney Injury (AKI) - MITT Population
Table 14.2-7.2 Subject Incidence of Post Surgery Major Adverse Kidney Event (MAKE) Collected on the AE CRF - MITT Population
Table 14.2-9.1 Subject Incidence of PostOp Creatinine Increase - Part 1 - MITT Population
Table 14.2-9.2 Subject Incidence of PostOp Creatinine Increase - Part 2 - MITT Population
Table 14.2-9.3 Subject Incidence of PostOp Creatinine Increase - Part 3 - MITT Population
Table 14.2-9.4 Subject Incidence of PostOp Creatinine Increase - Part 4 - MITT Population
Table 14.2-9.5 Subject Incidence of PostOp eGFR Decrease - Part 1 - MITT Population
Table 14.2-9.6 Subject Incidence of PostOp eGFR Decrease - Part 2 - MITT Population
Table 14.2-10.1 Analysis PostOp Proteinuria and Albuminuria - MITT Population
Table 14.2-10.2 Analysis PostOp Urine Albumin/Creatinine and Protein/Creatinine Ratios - MITT Population
Table 14.2-11 Subject Incidence of PostOp Creatinine Increase by 0.3 mg/dL, 0.5 mg/dL, 50% Increase from Baseline During Hospitalization - MITT Population
Table 14.2-12.1 Analysis of Change and Percent Change from Baseline to Each PostOp Visit in Urine Albumin Creatinine Ratio (UACR, mg/g) - MITT Population
Table 14.2-12.2 Analysis of Change and Percent Change from Baseline to Each PostOp Visit in Urine Protein Creatinine Ratio (UPCR, g/g) - MITT Population

Table 14.2-13.1.1 Analysis of Change and Percent Change from Baseline to Each PostOp Visit in Kidney Injury Molecule-1 (ng/mL) - MITT Population
Table 14.2-13.1.2 Analysis of Change and Percent Change from Baseline to Each PostOp Visit in Urine Creatinine-Normalized Kidney Injury Molecule-1 (ng/mg) - MITT Population
Table 14.2-13.1.3 Frequency Counts for Subjects Whose uCr-Normalized Kidney Injury Molecule-1 (ng/mg) > 2.38 - MITT Population
Table 14.2-13.2.1 Analysis of Change and Percent Change from Baseline to Each PostOp Visit in Cystatin C (ng/mL) - MITT Population
Table 14.2-13.2.2 Analysis of Change and Percent Change from Baseline to Each PostOp Visit in Urine Creatinine-Normalized Cystatin C (ng/mg) - MITT Population
Table 14.2-13.2.3 Frequency Counts for Subjects Whose uCr-Normalized Cystatin C (ng/mg) > 48.0 - MITT Population
Table 14.2-13.3.1 Analysis of Change and Percent Change from Baseline to Each PostOp Visit in Neutrophil Gelatinase Lipocal (ng/mL) - MITT Population
Table 14.2-13.3.2 Analysis of Change and Percent Change from Baseline to Each PostOp Visit in Urine Creatinine-Normalized Neutrophil Gelatinase Lipocal (ng/mg) - MITT Population
Table 14.2-13.3.3 Frequency Counts for Subjects Whose uCr-Normalized NGAL (ng/mg) > 94.4 - MITT Population
Table 14.2-14.1 Subject Counts by CKD and AKI Risk Factors- MITT Population
Table 14.2-14.2 Summary of Day 30 eGFR and Hospital Parameters by CKD - MITT Population
Table 14.2-14.3 Frequency Counts for Subjects who had 0.3mg/dL, 0.5mg/dL or 50% Increase in sCr by CKD - MITT Population
Table 14.2-14.4 Summary of Day 30 eGFR and Hospital Parameters by AKI Risk Factor - MITT Population
Table 14.2-14.5 Frequency Counts for Subjects who had 0.3, 0.5 or 50% increase in sCr by AKI Risk Factor - MITT Population
Table 14.2-15.1 Subject Incidence of AKI by No. of Baseline Risk Factors - Version 1 - MITT Population
Table 14.2-15.2 Subject Incidence of AKI by No. of Baseline Risk Factors - Version 2 - MITT Population
Table 14.2-15.3 Subject Incidence of AKI by No. of Baseline Risk Factors - Version 3 - MITT Population
Table 14.2-15.4 Composite of Single sCr >=0.3, 0.5 mg/dL or 50% Increase with Days on Ventilator >1, Days in ICU >X, Days in Hospital >Y - MITT Population
Listing 16.2-2.1.3 Subject Preconditioning Response Biomarker Composite Score (Avg Post Dose/Baseline) - MITT Population
Listing 16.2-2.3.1 Subject Sustained Urinary Retention During the First 3 Days Post Surgery Based on Urine Output - MITT Population
Listing 16.2-2.5.3 Subject Acute Kidney Injury Incidence and Severity - MITT Population
Listing 16.2-8.1 Patients with 50% Increase in Serum Creatinine in Hospital and Sustained Through Day 30 and, Day 60 or Day 90 - MITT Population
Listing 16.2-8.2 Patients with Serum Creatinine Increase in Hospital for 48 and 72 Hours - MITT Population
Listing 16.2-8.3 Patients with Serum Creatinine Increase in Hospital for 48 and 72 Hours and Sustained Through Day 30, and 60 or 90 - MITT Population
Listing 16.2-8.4 Patients with Serum Creatinine Increase in Hospital for 48 and 72 Hours, and eGFR Decrease at Day 30, and 60 or 90 - MITT Population
Listing 16.2-8.5 Patients with eGFR Decrease in Hospital for 48 and 72 Hours - MITT Population
Listing 16.2-8.6 Patients with eGFR Decrease in Hospital for 48 and 72 Hours, and Sustained at Day 30, and 60 or 90 - MITT Population
Listing 16.2-9.1 Patients with 15% Increase in PostOp Urine Protein or Albumin - MITT Population
Listing 16.2-9.2 Patients with 15% Increase in PostOp Urine Albumin/Creatinine and Protein/Creatinine Ratios - MITT Population
Figure 14.2-1.1 Spaghetti Plot of Creatinine (mg/dL) Over Time - MITT Population
Figure 14.2-1.2 Spaghetti Plot of eGFR (mL/min/1.73 m2) Over Time - MITT Population
Figure 14.2-1.3 Spaghetti Plot of KIM-1 (ng/mL) Over Time - MITT Population
Figure 14.2-1.4 Spaghetti Plot of NGAL (ng/mL) Over Time - MITT Population
Figure 14.2-1.5 Spaghetti Plot of Cystatin C (ng/mL) Over Time - MITT Population
Figure 14.2-3.1 Scatter Plot Matrix of Total No. of AKI Risk Factors, 0.3 mg/dL Increase in sCr for 48 Hours, Day 30 eGFR,Days on Ventilator, Days in Hospital, and Days in ICU - MITT Population

Figure 14.2-3.2 Scatter Plot with LOESS Curve of 0.3 mg/dL Increase in sCr any Time in Hospital over Total No. of AKI Risk Factors - MITT Population
Figure 14.2-3.3 Scatter Plot with LOESS Curve of 0.3 mg/dL Increase in sCr for 48 Hours in Hospital over Total No. of AKI Risk Factors - MITT Population
Figure 14.2-3.4 Scatter Plot with LOESS Curve of 0.5 mg/dL Increase in sCr any Time in Hospital over Total No. of AKI Risk Factors - MITT Population
Figure 14.2-3.5 Scatter Plot with LOESS Curve of 0.5 mg/dL Increase in sCr for 48 Hours in Hospital over Total No. of AKI Risk Factors - MITT Population
Figure 14.2-3.6 Scatter Plot with LOESS Curve of Day 30 eGFR over Total No. of AKI Risk Factors any Time in Hospital - MITT Population
Figure 14.2-3.7 Scatter Plot with LOESS Curve of Day 30 eGFR over 0.3 mg/dL Increase in sCr any Time in Hospital - MITT Population
Figure 14.2-3.8 Scatter Plot with LOESS Curve of Day 30 eGFR over 0.3 mg/dL Increase in sCr for 48 Hours in Hospital - MITT Population
Figure 14.2-3.9 Scatter Plot with LOESS Curve of Day 30 eGFR over 0.5 mg/dL Increase in sCr any Time in Hospital - MITT Population
Figure 14.2-3.10 Scatter Plot with LOESS Curve of Day 30 eGFR over 0.5 mg/dL Increase in sCr for 48 Hours in Hospital - MITT Population
Figure 14.2-3.11 Scatter Plot with LOESS Curve of Day 30 eGFR over Days in Hospital - MITT Population
Figure 14.2-3.12 Scatter Plot with LOESS Curve of Day 30 eGFR over Days on Ventilator - MITT Population
Figure 14.2-3.13 Scatter Plot with LOESS Curve of Day 30 eGFR over Days in ICU - MITT Population
Figure 14.2-4.1 Scatter Plot of PostOp Max(sCr) over PostOp Max(KIM-1) on Log_2 Scale
Figure 14.2-4.2 Scatter Plot of PostOp Max(sCr) over PostOp Max(Cystatin C) on Log_2 Scale
Figure 14.2-4.3 Scatter Plot of PostOp Max(sCr) over PostOp Max(NGAL) on Log_2 Scale

v3.0

Below tables, listings, and figures are added or modified for v3.0 as a result of SAP update.

Table 14.1-9 Summary of Important Protocol Deviations – Safety Population
Table 14.2-4.2 Subject Incidence of Revised Acute Kidney Injury (AKI) - MITT Population
Table 14.2-7.1 Subject Incidence of Major Adverse Kidney Events (MAKE) Post Surgery - MITT Population
Table 14.2-8.1 Analysis of Post Surgery Hospitalization Parameters by Surgery Type - MITT Population
Table 14.2-8.2 Analysis of Post Surgery Hospitalization Parameters by In/Outpatient Surgery Status - MITT Population
Table 14.2-8.3 Analysis of Post Surgery Hospitalization Parameters by CKD/Non-CKD Status - MITT Population
Table 14.2-8.4 Analysis of Post Surgery Hospitalization Parameters by No. of Baseline Risk Factors - MITT Population
Table 14.2-8.5 Analysis of Post Surgery Hospitalization Parameters by The Tertile of Baseline EUROSCORE - MITT Population
Table 14.2-8.6 Analysis of Post Surgery Hospitalization Parameters by The Tertile of Baseline STS Score - MITT Population
Table 14.2-8.7 Correlation Analysis between Hospital Parameters and Primary Composite and Component Endpoints – MITT Population
Table 14.2-8.8 Analysis of the Composite Score of Ventilator Days, ICU Days, and Hospital Days – MITT Population
Table 14.3-1.8 Select TEAEs of Interest, Overall and by Preferred Term – Safety Population
Table 14.3-1.9 Photosensitivity TEAEs, Overall and by Preferred Term – Safety Population
Listing 16.2-2.3.2 Subject Sustained Urinary Retention During the First 5 Days Post Surgery Based on AE Report - MITT Population
Listing 16.2-2.4 Subject Serum Creatinine and eGFR Assessments by Visit - MITT Population
Listing 16.2-2.5.1 Subject Incidence of Acute Kidney Injury PostOp Through Day 5 - MITT Population
Listing 16.2-2.5.2 Subject Incidence and Severity of Acute Kidney Injury PostOp Through Day 7 - MITT Population
Figure 14.2-3.1 Scatter Plot with LOESS Curve Fitting for Days on Ventilator Over GM of Max PreOp/Baseline Preconditioning Biomarkers by Treatment Group
Figure 14.2-3.2 Scatter Plot with LOESS Curve Fitting for Days in ICU Over GM of Max PreOp/Baseline Preconditioning Biomarkers by Treatment Group

Figure 14.2-3.3 Scatter Plot with LOESS Curve Fitting for Days in Hospital Over GM of Max PreOp/Baseline Preconditioning Biomarkers by Treatment Group
Figure 14.2-4.1 Scatter Plot with LOESS Curve Fitting for Days on Ventilator Over Max PreOp/Baseline in Serum HO-1 by Treatment Group
Figure 14.2-4.2 Scatter Plot with LOESS Curve Fitting for Days in ICU Over Max PreOp/Baseline in Serum HO-1 by Treatment Group
Figure 14.2-4.3 Scatter Plot with LOESS Curve Fitting for Days in Hospital Over Max PreOp/Baseline in Serum HO-1 by Treatment Group
Figure 14.2-5.1 Scatter Plot with LOESS Curve Fitting for Days on Ventilator Over Max PreOp/Baseline in Serum IL-10 by Treatment Group
Figure 14.2-5.2 Scatter Plot with LOESS Curve Fitting for Days in ICU Over Max PreOp/Baseline in Serum IL-10 by Treatment Group
Figure 14.2-5.3 Scatter Plot with LOESS Curve Fitting for Days in Hospital Over Max PreOp/Baseline in IL-10 by Treatment Group