Randomized Trial of Transcatheter Valve-in-Valve Versus Redo-Surgery for Bioprosthetic Valve Dysfunction

ClinicalTrials.gov: NCT04402931
(date of registration: May 21, 2020)

STATISTICAL ANALYSIS PLAN

SAP version: 1.0, July 31st, 2025
Study protocol version: 3.0, October 16th, 2022

1.0 Introduction

Transcatheter mitral valve-in-valve (mViV) implantation is recommended as an alternative treatment for high-risk or inoperable patients with deteriorated surgical mitral bioprostheses that require a reintervention [1]. Observational data suggest favorable procedural safety and early hemodynamic outcomes [2-4], and recent meta-analyses comparing mViV and rMVR have shown equivalent mortality but lower incidences of stroke, major bleeding, and acute kidney injury with mViV [5-11]. Most available data are derived from observational studies subject to selection bias, heterogeneous follow-up, and incomplete adjustment for confounding. Prospective and randomized studies comparing both treatments remain unavailable.

The present study is designed to compare the safety and efficacy of transcatheter mitral ViV implantation with conventional redo-mitral valve surgery in a prospective randomized setting. This Statistical Analysis Plan (SAP) prespecifies all analyses before database lock.

2.0 Study Objectives

The study aims to evaluate the comparative clinical effectiveness and safety of transcatheter mitral valve-in-valve (mViV) treatment versus redo-surgical mitral valve replacement (rSMVR) in patients with bioprosthetic mitral valve dysfunction.

2.1 Primary Objective

To evaluate the safety and efficacy of transcatheter balloon-expandable mViV compared with rSMVR.

2.2 Secondary Objectives

To compare clinical outcomes after mViV and rSMVR, including the occurrence of cardiovascular death, stroke with residual deficit (disabling stroke), major vascular complications, life-threatening and major bleeding, atrial fibrillation, acute kidney injury (AKIN stages 2 & 3), reoperation, rehospitalization for cardiovascular causes and health related quality of life, and echocardiographic and tomographic parameters related to prosthetic valve thrombosis and structural valve deterioration during follow-up.

3.0 Study Design

Prospective, multicenter, randomized, open-label clinical trial enrolling patients aged ≥18 years with symptomatic severe dysfunction of a mitral bioprosthesis requiring intervention and considerable eligible by the Heart Team for either mitral ViV implantation or redo surgical mitral valve replacement. Clinical, echocardiographic, and computed tomography outcomes are assessed longitudinally.

4.0 Randomization and Blinding

Randomization is performed using a centralized electronic system with concealed allocation. Due to the nature of the interventions, blinding of patients and treating physicians is not feasible. Endpoint adjudication will be performed by a blinded clinical events committee.

5.0 Study Endpoints

5.1 Primary Endpoint

The primary endpoint is defined as time to first occurrence of all-cause death or disabling stroke through 12 months after the index procedure.

5.2 Secondary Endpoints

Secondary endpoints include individual components of the primary endpoint, safety outcomes at 30 days, rehospitalization due to cardiovascular causes at 12 months, valve-related complications assessed during imaging follow-up, and health-related quality of life measured by the EQ-5D-5L questionnaire. Safety endpoints at 30 days will be analyzed as time-to-event outcomes up to 30 days. Valve-related complications assessed at predefined visits will be analyzed using cumulative incidence or cross-sectional comparisons as appropriate.

Endpoints are defined according to standardized clinical definitions consistent with Mitral Valve Academic Research Consortium recommendations [12] (see Table 1 below).

Table 1 – MVARC definitions

Mortality Cardiovascular vs. non-cardiovascular mortality	**A. Cardiovascular mortality** Any of the following contributing conditions: • Heart failure (subclassified into left ventricular vs. right ventricular dysfunction) • Myocardial infarction • Major bleeding • Thromboembolism • Stroke • Arrhythmia and conduction system disturbance • Cardiovascular infection and sepsis (e.g., mediastinitis • and endocarditis) • Tamponade • Sudden, unexpected death • Other cardiovascular • Device failure • Death of unknown cause (adjudicated as cardiovascular) **B. Non-cardiovascular mortality** • Any death in which the primary cause of death is clearly related • to another condition: • Non-cardiovascular infection and sepsis (e.g., pneumonia) • Renal failure • Liver failure • Cancer • Trauma • Homicide • Suicide • Other non-cardiovascular
Hospitalization	**Definition** Admission to an inpatient unit or ward in the hospital for ≥24 h, including an emergency department stay. Hospitalizations planned for pre-existing conditions are excluded unless there is worsening of the baseline condition. Hospitalization is Further Subclassified as: I. **Heart failure hospitalization:** Both of the following additional criteria are present: • Symptoms, signs and/or laboratory evidence of worsening heart failure

	• Administration of intravenous or mechanical heart failure therapies. Patients hospitalized with heart failure are further subclassified as: **IA. Primary (cardiac related)** heart failure hospitalization **IB. Secondary (non-cardiac related)** heart failure hospitalization **II. Other cardiovascular hospitalization:** such as for coronary artery disease, acute myocardial infarction, hypertension, cardiac arrhythmias, cardiomegaly, pericardial effusion, atherosclerosis, stroke, or peripheral vascular disease without qualifying heart failure **III. Non-cardiovascular hospitalization:** not due to heart failure or other cardiovascular causes, as defined above.
Stroke	**<u>Diagnostic criteria</u>** Acute episode of a focal or global neurological* deficit ≥24 h OR < 24 h if available neuroimaging documents a new intracranial or subarachnoid haemorrhage (haemorrhagic stroke) or central nervous system infarction (ischaemic stroke) OR the neurological deficit results in death. * At least 1 of the following: A. Change in the level of consciousness B. Hemiplegia, hemiparesis, numbness, or sensory loss affecting 1 side of the body C. Dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke In addition, there is no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumour, trauma, infection, hypoglycaemia, peripheral lesion, pharmacological influences) as determined by or in conjunction with the designated neurologist* Confirmation of the diagnosis of stroke requires at least 1 of the following: I. Neurologist or neurosurgical specialist, or II. Neuroimaging procedure (CT scan or brain MRI) **<u>Stroke timing classification</u>** ***I. Periprocedural*** if it occurs within 30 days of the intervention, or if beyond 30 days in the patient not yet discharged. A periprocedural stroke may be further considered immediate if it occurs within 24 h

	of the procedure or within 24 h of awakening from general anaesthesia if beyond 24 h. **II. Nonperiprocedural** if it occurs beyond 30 days after the intervention and after the patient has been discharged. **<u>Stroke aetiology classification</u>** **I. Ischaemic:** an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue **II. Haemorrhagic:** an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage **III. Undetermined:** if there is insufficient information to allow categorization as ischaemic or haemorrhagic. **<u>Stroke severity</u>** is further classified as **I. Disabling stroke:** an mRS score ≥2 at 90 days plus an increase in ≥1 mRS category from the pre-stroke baseline **II. Non-disabling stroke:** an mRS score < 2 at 90 days or without an increase ≥1 mRS category from the pre-stroke baseline
Myocardial infarction	**I. Periprocedural MI** (≤48 h after the index procedure) **A.** In patients with normal baseline CK-MB (or cTn): The peak CK-MB measured within 48 h of the procedure rises to ≥10x the local laboratory ULN plus new ST-segment elevation or depression of ≥1 mm in ≥2 contiguous leads (measured 80 ms after the J-point), or to ≥5x ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the PCI rises to ≥70x the local laboratory ULN plus new ST-segment elevation or depression of ≥1 mmin ≥2 contiguous leads (measured 80 ms after the J-point), or ≥35x ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB. **B.** In patients with elevated baseline CK-MB (or cTn): The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus, new ECG changes as described. **II. Spontaneous MI** (.48 h after the index procedure)‡

	Detection of rise and/or fall of cardiac biomarkers (preferably cTn) with at least 1 value above the 99th percentile URL (or ULN in the absence of URL) together with at least 1 of the following: **A.** Symptoms of ischaemia **B.** ECG changes indicative of new ischaemia (new ST-segment or T-wave changes or new LBBB) or new pathological Q waves in ≥2 contiguous leads **C.** Imaging evidence of a new loss of viable myocardium or new wall motion abnormality **III. MI associated with sudden, unexpected cardiac death** Sudden cardiac death or cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST-segment elevation or new LBBB and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurs before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood **IV. Pathological findings of an acute myocardial infarction**
Access site and vascular complications	**I. Vascular Complications** **A. Major access site vascular complications,** including: • Aortic dissection or aortic rupture, or • Access site-related arterial or venous injury (dissection, stenosis, ischaemia, arterial, or venous thrombosis including pulmonary emboli, perforation, rupture, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, atrial septal defect), irreversible nerve injury, or compartment syndrome resulting in death; hemodynamic compromise; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischaemia; or neurological impairment, or • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage, or • Unplanned endovascular or surgical interventions resulting in death; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischaemia; or neurological impairment **B. Minor access site vascular complications,** including: • Access site arterial or venous injury (dissection, stenosis, arterial, or venous thrombosis including pulmonary emboli, ischaemia, perforation, rupture, arterio-venous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, atrial septal defect‡) not resulting in death; life-threatening, extensive, or major bleeding (MVARC scale); visceral ischaemia; or neurological impairment, or

	• Distal embolization treated with embolectomy and/or thrombectomy not resulting in amputation or irreversible end-organ damage, or • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication, or • Vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) **<u>II. Cardiac structural complications due to access-related issues</u>** **A. Major cardiac structural complications,** including: • Cardiac perforation or pseudoaneurysm resulting in death, life-threatening bleeding, hemodynamic compromise, or tamponade, or requiring unplanned surgical or percutaneous intervention **B. Minor cardiac structural complications,** including: • Cardiac perforation or pseudoaneurysm not meeting major criteria
Bleeding complications	**<u>MVARC Primary Bleeding Scale</u>** **I. Minor** Any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that meets ≥1 of the following: requiring nonsurgical medical intervention by a health care professional; leading to hospitalization or increased level of care; prompting evaluation; or requires 1 or 2 U of whole blood or packed RBC transfusion and otherwise does not meet criteria for major, extensive, or life-threatening bleeding. **II. Major** Overt bleeding either associated with a drop in the haemoglobin of ≥3.0 g/dl‡ or requiring transfusion of ≥3 U of whole blood or packed RBCs AND does not meet criteria of life-threatening or extensive bleeding. **III. Extensive** Overt source of bleeding with drop in haemoglobin of ≥4 g/dl or whole blood or packed RBC transfusion ≥4 U within any 24-h period, or bleeding with drop in haemoglobin of ≥6 g/dl or whole blood or packed RBC transfusion ≥4 U (BARC type 3b) within 30 days of the procedure. **IV. Life-threatening**

	Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating surgery or intervention, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or hypotension (systolic blood pressure <90 mm Hg lasting >30 min and not responding to volume resuscitation) or requiring significant doses of vasopressors or surgery. **V. Fatal** Bleeding adjudicated as being a proximate cause of death. Severe bleeding adjudicated as being a major contributing cause of a subsequent fatal complication, such as MI or cardiac arrest, is also considered fatal bleeding. **Modified BARC Bleeding Scale** **Type 0** No bleeding. **Type 1** Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional. May include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional. **Type 2** Any overt,† actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet ≥1 of the following: requiring nonsurgical medical intervention by a health care professional, leading to hospitalization or increased level of care, or prompting evaluation. **Type 3a** Overt bleeding plus haemoglobin drop of 3 to <5 g/dl‡ (provided drop is related to bleed) Any transfusion with overt bleeding **Type 3b** Overt bleeding plus haemoglobin drop ≥5 g/dl‡ (provided drop is related to bleed) Cardiac tamponade

	Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid) Bleeding requiring IV vasoactive agents **Type 3c** Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation but does include intraspinal bleeding) Subcategories confirmed by autopsy, imaging, or lumbar puncture Intraocular bleeding compromising vision **Type 4 (periprocedural)** Perioperative intracranial bleeding ≤48 h Reoperation after closure of incision site for the purpose of controlling bleeding Transfusion of ≥5 U whole blood or packed RBCs within 48-h period of the index procedure Chest tube output ≥2 l within 24-h period **Type 5a:** Probable fatal bleeding. No autopsy or imaging confirmation but clinically suspicious. **Type 5b:** Definite fatal bleeding. Overt bleeding, autopsy, or imaging confirmation.
Definitions **and stages of acute** **renal injury**	Maximal change in serum Creatinine (sCr) from baseline to 7 days post-procedure. **Stage 1** Increase in sCr to 150%–199% (1.50 – 1.99x increase vs. baseline), increase of ≥ 0.3 mg/dl (≥ 26.4 mmol/l) within 48 h, or urine output < 0.5 ml/kg/h for ≥6 h but <12 h **Stage 2** Increase in sCr to 200%–299% (2.00–2.99x increase vs. baseline) or urine output <0.5 ml/kg/h for ≥12 h but < 24 h **Stage 3** Increase in sCr to ≥300% (>3.0x increase vs. baseline), sCr of ≥4.0 mg/dl (≥354 mmol/l) with an acute increase of ≥0.5 mg/dl (44 mmol/l), urine output <0.3 ml/kg/h for ≥24 h, or anuria for ≥12 h; patients receiving renal replacement therapy are considered stage 3 irrespective of other criteria

New York Heart Association Classification (NYHA)	**Functional Capacity** **I** Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. **II** Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. **III** Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. **IV** Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Bioprosthetic Valve Dysfunction	**Structural BVD** • Intrinsic permanent changes to the prosthetic valve leaflets or stent, including leaflet wear and tear, disruption, flail leaflet, leaflet fibrosis and/or calcification, stent fracture, or deformation. <u>*Subclinical:*</u> Imaging findings of permanent changes to the leaflets or stent with absent or mild hemodynamic changes AND no symptoms/sequelae. <u>*Clinically significant:*</u> 1) Stage 2 or 3 BVD with clinically expressive criteria (new-onset or worsening symptoms, LV dilation/hypertrophy/dysfunction, or pulmonary hypertension); 2) in the absence of symptoms or sequelae, both hemodynamic valve deterioration Stage 2 or 3 and confirmatory imaging of morphologic leaflet/stent abnormalities and/or confirmatory invasive hemodynamic assessment of valve hemodynamic dysfunction.
Severe Mitral Bioprosthetic Valve Dysfunction	**Mitral stenosis:** Main criteria for the diagnosis of significant mitral stenosis are a mean gradient >10 mm Hg at a normal heart rate, a PHT >200 msec, a DVI >2.5, and an EOA <1 cm^2. **Mitral Regurgitation**

	Doppler parameters • Color flow jet area: large central jet (usually >8 cm2 or >50% of LA area) • Pulmonary venous flow: systolic flow reversal *Quantitative parameters* • Vena contracta width (cm) ≥ 0.7 • Regurgitant Volume ≥60 ml • Regurgitant Fraction ≥50% • Effective Regurgitant Orificce Area ≥0.40 cm2

Adapted from references 12 (clinical definitions) and 13 (echocardiographic definitions).

6.0 Patient Selection

6.1 Inclusion criteria

- Age > 18 years old.
- Symptoms of heart failure NYHA class > II.
- Severe mitral bioprosthetic dysfunction defined by echocardiography.
- Heart team agree on eligibility including assessment that mViV and rMVR are suitable.
- The study patient or the study patient's legal representative informed of the nature of the study, agreed to its provisions and provided written informed consent as approved by the Institutional Review Board (IRB) center.
- The study patient agreed to comply with all required post-procedure follow-up visits including annual visits through 10 years.
- Heart team agreed on treatment strategy for concomitant coronary disease (if present).

- Patient agreed to undergo rMVR if randomized to control treatment.

6.2 Exclusion criteria

- Heart Team assessment of inoperability (including examining cardiac surgeon).
- Hostile chest.
- Acute myocardial infarction < 1 month before the intended treatment [WHO definition].
- Concomitant, severe valvular disease (aortic, tricuspid or pulmonic) requiring surgical intervention.
- Mitral mechanical prosthesis or valve rings.
- Preexisting mechanical or bioprosthetic valve dysfunction in other position.
- Complex CAD: unprotected LM, Syntax > 32 (in the absence of prior revascularization).
- Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant CAD). Implantation of a permanent pacemaker is not an exclusion criterion.
- Patients with planned concomitant surgical or transcatheter ablation for atrial fibrillation.
- Leukopenia (WBC < 3000 cell/mL), acute anemia (Hgb< 9 g/dL), thrombocytopenia (Pht< 50,000 cell/mL).
- Hypertrophic cardiomyopathy with or without obstruction (HOCM).

- Predicted neo-LVOT area <170 mm² without feasible augmentation strategies.
- Severe ventricular dysfunction with left-ventricular ejection fraction (LVEF) < 20%.
- Echocardiographic evidence of a mobile intracardiac mass, thrombus or vegetation.
- Active upper gastrointestinal (GI) bleeding within 3 months (90 days) prior to procedure.
- A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.
- Clinically or neuroimaging confirmed stroke or TIA within 3 months of the procedure.
- Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy at screening.
- Estimated life expectancy < 12 months due to activity malignancies, severe hepatic dysfunction (Child-Pugh class C), severe COPD (FEV_1 <30% predicted) or others.
- Currently participating in an investigational drug or another device study.
- Active bacterial endocarditis within 6 months of procedure.
- Current pregnancy or intention to become pregnant during study period.

Abbreviations: CAD, coronary artery disease; LM, left main; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; LV, left ventricular; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; ViV, valve-in-valve.

7.0 Follow-up Schedule

Follow-up visits are scheduled at 30 days, 3 months, 12 months, and annually up to 10 years according to the protocol.

8.0 Sample Size Determination

The sample size calculation assumes superiority of mitral ViV compared with surgery for the composite primary endpoint at 12 months, with estimated event rates of 8% and 25%, respectively. Available evidence comparing both treatments were minimal at the time of the protocol design in 2018. Therefore, the mortality rates were estimated from descriptive studies published between 2012 and 2017 - which represented the most contemporary data available at the time of protocol development. These studies report on the 1-year follow-up after mViV or rSMVR separately [14-18]. Moreover, stroke rates beyond 30-days were not reported systematically in the literature, so historical data from participant centers were used. Assuming a two-sided alpha level of 0.05 and 80% power, a total of 150 patients is required, with 1:1 randomization.

9.0 Analysis Populations

Analyses will be performed according to modified intention-to-treat (mITT) and intention-to-treat (ITT) populations. The modified intention-to-treat population was prespecified as the primary efficacy population to account for differences in waiting time between treatment strategies that could introduce bias in post-randomization event

accrual. The index date for the mITT population will be the procedure date. Intercurrent events, including crossover or treatment delay, will not alter treatment assignment in the primary analysis. The primary analysis will follow the modified intention-to-treat principle. The ITT population is defined as all randomized patients followed from the randomization date, rather than procedure. All participants will be analyzed in the group as he was assigned independently of the procedure have been done, or any protocol deviations. The per protocol (PP) population is defined as the mITT population and without major protocol deviations.

10.0 Statistical Methods

All statistical tests will be two-sided with a significance level of 0.05. Results will be presented with 95% confidence intervals. No formal adjustment for multiplicity will be performed for secondary endpoints; analyses of secondary endpoints will therefore be considered exploratory.

10.1 Descriptive Analyses

Continuous variables will be summarized as mean ± standard deviation or median (interquartile range), according to distribution. Categorical variables will be summarized as counts and percentages.

10.2 Primary Efficacy Analysis

The primary analysis will be conducted in the modified intention-to-treat population using a Cox proportional hazards model. Primary analysis will be conducted in mITT population using procedure time as index date. Hazard Ratios will be presented with 95% confidence intervals.

10.3 Time-to-Event Analyses

Kaplan–Meier estimates will be used to describe cumulative event incidence. Hazard ratios will be derived from Cox proportional hazards models. The proportional hazards assumption will be evaluated using Schoenfeld residuals and graphical methods. In the presence of nonproportional hazards, treatment effects will be summarized using Greenwood z tests derived from the Kaplan Meier estimates at 30 days and 12 months.

10.4 Secondary Endpoint Analyses

Secondary time-to-event endpoints will be analyzed using methods consistent with the primary analysis. For nonfatal secondary endpoints in which death may act as a competing risk, sensitivity analyses using Fine–Gray subdistribution hazard models will be performed. Quality-of-life outcomes will be analyzed using linear regression models adjusted baseline EQ-5D-5L score.

Clinical endpoints at 30 days and the distribution of New York Heart Association (NYHA) functional class at 3 and 12 months were compared using Fisher's exact test.

Echocardiography measurements will be analysed by linear regression models adjusted for baseline values. Group comparisons at wach visit will be computed between groups with 95% confidence intervals. Results may be presented in mean profile graphs.

Time of hospitalization and time in ICU after de procedure will be compared between groups by Mann-Whitney tests.

10.5 Sensitivity analysis

All primary and secondary endpoints will be evaluated at ITT and PP population as sensitivity analysis.

Sensitivity analysis using restricted mean survival time differences at prespecified time points in addition to hazard ratios may also be presented.

11.0 Interim Analysis

No formal interim efficacy analyses will be performed; therefore, no alpha-spending adjustment is planned.

12.0 Missing Data

Time-to-event analyses will use censoring at the last available follow-up. The anticipated rate of missing data for the primary endpoint is expected to be minimal given active follow-up and vital status ascertainment. No formal imputation procedures are planned.

13.0 Statistical Software and Reproducibility

All analyses will be conducted using R (R Foundation for Statistical Computing, Vienna, Austria). All statistical code will be version-controlled and archived prior to unblinding of the primary results to ensure reproducibility.

14.0 Adverse Events Reporting

Adverse and serious adverse events not included as study endpoints will be summarized descriptively and presented comparatively between treatment groups.

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