Clinical Investigational Plan

Study Title: Edwards EWJ-202 **T**ranscatheter Tricuspid Valve **R**eplacement System: **I**nvestigation of **S**afety and **C**linical **E**fficacy using a **N**ovel **D**evice in patients with at least severe tricuspid regurgitation in **JAPAN**

Short Title: TRISCEND JAPAN

Investigational Device Identification Code: EWJ-202

Study number: 2021-12

Sponsor: Edwards Lifesciences Japan LLC

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Confidentiality

The information contained in this study protocol is intended for the principal investigator, sub-investigator(s), clinical research coordinator(s), study sites, and those who are directly involved in this study. Therefore, the information contained here must not be disclosed or leaked to any third party not involved in this study, except to the extent necessary to explain to person participating in the study. It must not be used to any purpose other than this study without the written authorization from Edwards Lifesciences Japan LLC.

This trial will be conducted in compliance with the "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (Act No. 145 of 1960), ethical principles based on the Declaration of Helsinki and the Ordinance of the Ministry of Health and Welfare No. 36 "Ministerial Ordinance on Good Clinical Practice (GCP) for Medical Devices" (March 23, 2005) as well as the Ordinance of Ministry of Health, Labour and Welfare No. 68 "Ministerial Ordinance on Good Clinical Practice for Drugs" (March 31, 2009) and related notification as well as this study protocol.

List of Abbreviations

Abbreviation	English
6MWD	6 Minute Walk Distance
6MWT	6 Minute Walk Test
ACC	American College of Cardiology
ACE	Angiotensin Converting Enzyme Inhibitor
ACT	Activated Clotting Time
AHA	American Heart Association
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
APS	Acute Procedure Success
aPTT	Activated Partial Thromboplastin Time
ARB	Angiotensin II Receptor Blocker
ARNI	Angiotensin Receptor Neprilysin Inhibitor
ASA	Acetylsalicylic Acid
ASD	Atrial Septal Defect
AST	Asparate Aminotransferase
AT	As-Treated
BARC	Bleeding Academic Research Consortium
BMI	Body Mass Index
BNP	human Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
CCU	Coronary Care Unit
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CI	Confidence Interval
CK	Creatine Kinase
CK-MB	Creatine Kinase MB isoenzyme
CMR	Cardiac Magnetic Resonance
COPD	Chronic Obstructive Pulmonary Disease
CRT	Cardiac Resynchronization Therapy
CSC	Central Screening Committee
CSHA	Canadian Study of Health and Aging
CT	Computed Tomography
DMC	Data Monitoring Committee
DOAC	Direct Oral Anticoagulant
DSMB	Data Safety Monitoring Board
dP/dt	---
DRI	Direct Renin Inhibitor
DVT	Deep Vein Thrombosis
EACTS	European Association for Cardio-Thoracic Surgery
e-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGRF	estimated Gemerular FItration Rate
EQ-5D-5L	EuroQol – 5 Dimension – 5 Level
EROA	Effective Regurgitant Orifice Area
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FTR	Functional Tricuspid Regurgitation
GCP	Good Clinical Practice
GDMT	Guideline Directed Medical Therapy
HFpEF	Heart Failure with preserved Ejection Fraction
ICD	Implantable Cardioverter Defibrillator
ICU	Intensive Care Unit
INR	International Normalized Ratio

Abbreviation	English
ISO	Internatinal Organization for Standard
ITT	Intention-to-Treat
KCCQ	The Kansas City Cardiomyopathy Questionnaire
LVEF	Left Ventricular Ejection Fraction
MAE	Major Adverse Event
MDR	Medical Device Regulation
MRA	Mineralocorticoid Receptor Antagonist
mRS	modified Rankin Scale
MV	Mitral Valve
MVARC	Mitral Valve Academic Research Consortium
MVR	Mitral Valve Replacement
NT-proBNP	N-terminal pro-Brain Natriuretic Peptide
NYHA	New York Heart Association
OAC	Oral Anticoagulant
OMT	Optimal Medical Therapy
PACU	Postanesthesia Care Unit
PASP	Pulmonary Artery Systolic Pressure
PCI	Percutaneous Coronary Intervention
PDE III	Phosphodiesterase III
PE	Pulmonary Embolism
PISA	Proximal Isovelocity Surface Area
PP	Per Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin
PVL	Paravalvular Leak
PVR	Pulmonary Vascular Resistance
QOL	Quality of Life
RBC	Red Blood Cell
RI	Roll-in
RVFAC	Right Ventricular Fractional Area Change
SF-36	Short Form 36-item Health Survey
STS	Society of Thoracic Surgeons
TAPSE	Tricuspid Annular Plane Systolic Excursion
TAVR	Transcatheter Aortic Valve Replacement
TIA	Transient (cerebral) Ischemic Attack
TEE	Transesophageal Echocardiography
TTE	Transthoracic Echocardiography
TTVR	Transcatheter Tricuspid Valve Replacement
TTR	Time in Therapeutic Range
VARC	Valve Academic Research Consortium
VC	Vena Contracta
VCA	Vena Contracta Area
VKA	Vitamin K Antagonist
TR	Tricuspid Regurgitation
WBC	White Blood Cell
βhCG	human Chorionic Gonadotropin beta-subunit
GGT	Gamma-Glutamyl Transferase

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Protocol Synopsis

Study Title: A Clinical Study of Transcatheter Tricuspid Valve Replacement System EWJ-202 in Patients with Severe Tricuspid Regurgitation

Investigational device Identification Code: EWJ-202

Protocol Identification Code: 2021-12

Item	Details
Objective	The objective of this trial is to confirm the safety and effectiveness of EWJ-202 under the healthcare environment in Japan in patients with at least severe tricuspid regurgitation despite medical therapy.
Trial Design	Prospective, open, non-randomized, multicenter, clinical trial
Primary endpoints (Co-primary)	[Safety and Effectiveness Endpoint] All-cause mortality (1-year post procedure) Heart failure hospitalization (1-year post procedure)
Secondary endpoints	[Effectiveness endpoints] 1. TR grade (30 days, 6 months, 1 year, and annually until 5 years) 2. NYHA Classification (30 days, 6 months, 1 year, and annually until 5 years) 3. QOL (30 days, 6 months, 1 year,2 years) - SF-36 - KCCQ - EQ-5D-5L 4. 6MWD (30 days, 6 months, 1 year,2 years) [Safety endpoint] 1. Composite endpoint of Major Adverse Events (MAE) (30 days) - Cardiovascular mortality - Myocardial infarction - Stroke - New need for renal therapy - Severe bleeding - Non-elective tricuspid valve re-intervention (percutaneous or surgical) - Major access site and vascular complications - Major cardiac structural complications due to access-related issues - Device-related pulmonary embolism - Arrhythmia and conduction disorder requiring permanent pacing 2. Individual components of MAE (30 days, 6 months, 1year, and annually until 5 years) 3. All-cause mortality (30 days, 6 months, 1 year, and annually until 5 years) 4. Number of heart failure hospitalizations (30 days, 6 months, 1year, and annually until 5 years) 5. All-cause hospitalizations (30 days, 6 months, 1 year, and annually until 5 years) 6. Durable right ventricular assist device (RVAD) implantation or heart transplant (30 days, 6 months, 1 year, and annually until 5 years) 7. Tricuspid valve surgery or percutaneous tricuspid intervention (30 days, 6 months, 1year, and annually until 5 years) 8. Need for paracentesis (30 days, 6 months, 1year, and annually until 5 years)
Exploratory endpoints	[redacted]

Item	Details
Additional outcomes	[redacted]
Number of Planned Subjects	Main Cohort (Evaluable): 45 patients Roll in Cohort: up to 24 patients (up to 3 patients/site)
Investigational Device	EWJ-202 is composed of the following components: - Bioprosthetic Heart Valve - Delivery System - Loading System - Dilator kit - Stabilizer - Stabilizer Base - Stabilizer Plate
Target Population	Patients with at least severe tricuspid regurgitation
Inclusion Criteria	Patients enrolled must meet ALL of the following criteria: 1. Age ≥ 18 years old at the time of consent 2. Despite medical therapy (OMT) per the Local Heart Team, patient has signs of TR (ascites, edema, etc), symptoms from TR*, or prior heart failure hospitalization from TR Note: Patient must be on OMT per the local heart team at the time of TR assessment for trial eligibility (TTE). Medical therapy includes stable diuretic medications, unless patient has documented

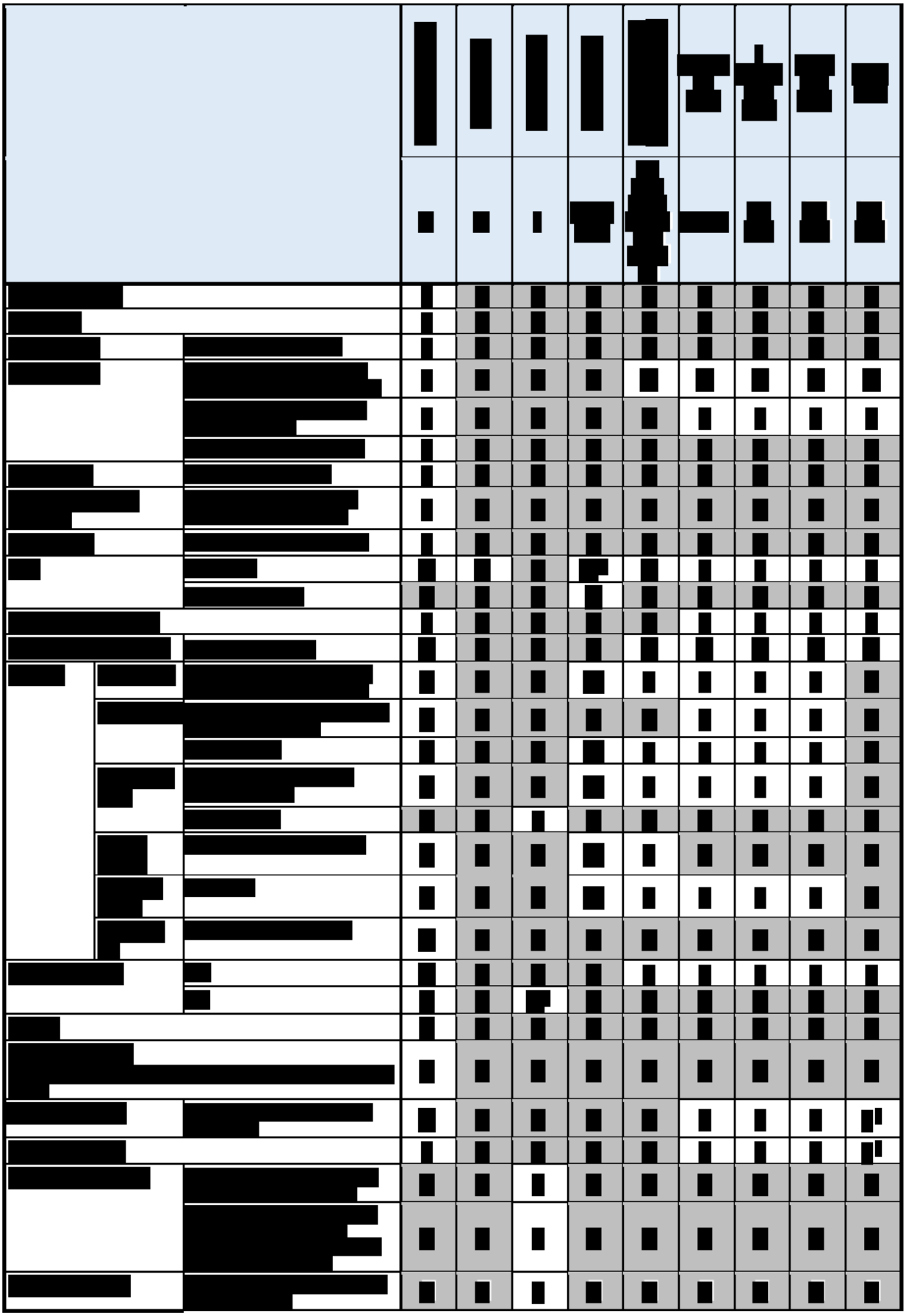
Item	Details
Inclusion Criteria (continued)	history of intolerance. Oral diuretic doses must be stable (no decrease of more than ½ or increase of 2x) in the 7 days prior to the baseline/screening TTE. Efforts should be made to keep oral diuretic doses stable after the TTE *, include, but are not limited to, patient classification as NYHA class II, III, or IVa, shortness of breath, fatigue, abdominal swelling, indigestion due to venous congestion of the gastrointestinal tract, etc. 3. Functional and/or degenerative TR graded as at least severe on a transthoracic echocardiogram (assessed by the echo core lab using a 5-grade classification) 4. The Local Heart Team determines that the patient is appropriate for transcatheter tricuspid valve replacement 5. Patient is willing and able to comply with all specified study evaluations and provides written informed consent
Exclusion Criteria	Patients must not meet ANY of the following criteria: 1. Anatomy precluding proper EWJ-202 delivery, deployment and/or function. (Assessed by echo core lab and/or sponsor) 2. LVEF < 25% (Assessed by echo core lab) 3. Evidence of severe right ventricular dysfunction (Assessed by echo core lab) 4. Any of the following pulmonary pressure parameters: (a) Pulmonary arterial systolic pressure (PASP) >60 mmHg by echo doppler (unless right heart catheterization [RHC] demonstrates PASP ≤70 mmHg) (Assessed by echo core lab) (b) PASP > 70 mmHg by RHC (Assessed by site) (c) Pulmonary Vascular Resistance (PVR) >5 Wood units by RHC (unless PVR ≤5 Wood units and systolic BP >85 mmHg after vasodilator challenge). 5. Previous tricuspid surgery or intervention 6. Presence of trans-tricuspid pacemaker or defibrillator lead with any of the following: (a) Implanted in the RV within the last 90 days† (b) Patient is pacemaker dependent on trans-tricuspid lead without alternative pacing option (c) Has delivered appropriate ICD therapy Note: Patients with RV lead extraction are required to wait 30 days prior to the baseline/screening TTE 7. Severe aortic, mitral and/or pulmonic valve stenosis and/or regurgitation. (Assessed by echo core lab) Note: Patients with concomitant mitral or aortic or pulmonic and tricuspid valve disease will have the option of getting their respective valve treated, and wait 60 days post transcatheter or 90 days after surgical treatment prior to being reassessed for the study 8. Active endocarditis within the last 90 days† or infection requiring antibiotic therapy (oral or intravenous) within the last 30 days† 9. Hemodynamically significant pericardial effusion 10. Significant intra-cardiac mass, thrombus, or vegetation (Assessed by echo core lab) Note: Chronic scarred LV apical or LAA thrombi can be considered. 11. Clinically significant, untreated coronary artery disease requiring revascularization, evidence of acute coronary syndrome, recent myocardial infarction within the last 30 days†

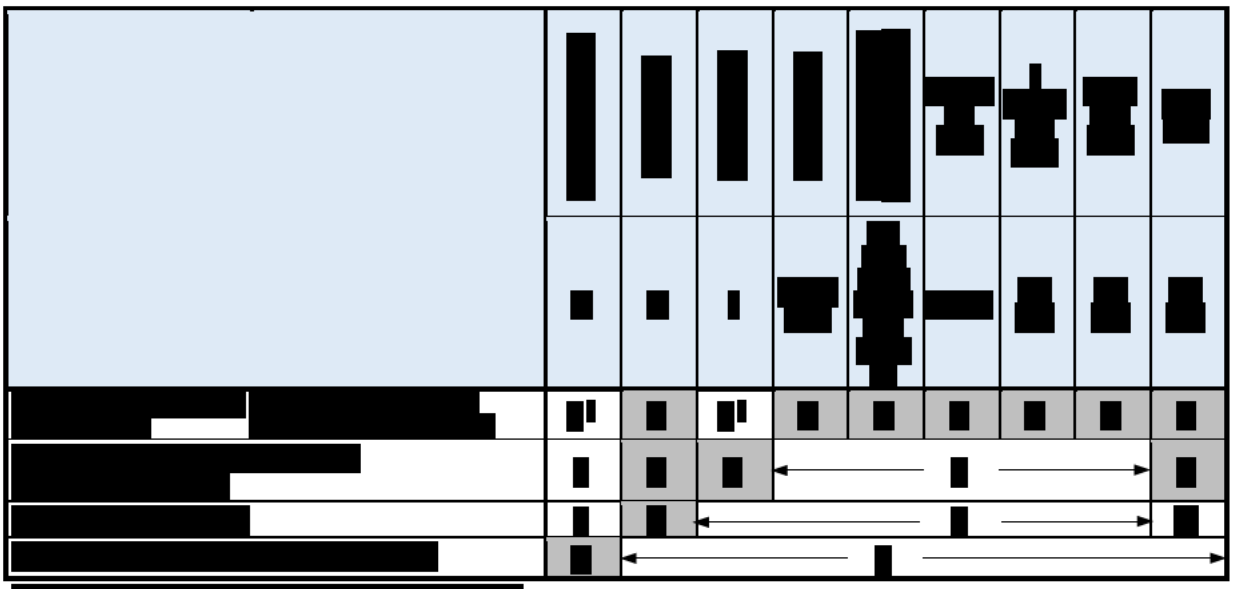
Item	Details
Exclusion Criteria (Continued)	12. Any of the following cardiovascular procedures: (a) Percutaneous coronary, intracardiac, or endovascular intervention within the last 30 days† Note: Intracardiac intervention includes, but is not limited to: left atrial appendage occlusion, ASD closure, AF ablation (b) Carotid surgery with in the last 30 days† (c) Direct current cardioversion within the last 30 days† (d) Leadless RV pacemaker implant within the last 30 days† (e) Cardiac surgery within the last 90 days† 13. Known history of untreated severe symptomatic carotid stenosis (>50% by ultrasound) or asymptomatic carotid stenosis (>70% by ultrasound) 14. Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months (365 days) †, or any planned percutaneous cardiac procedures within the next 90 days † 15. Hypotension (systolic pressure < 90 mmHg) or requirement for inotropic support or hemodynamic support within the last 30 days† 16. Patient with refractory heart failure requiring advanced intervention (i.e. patient has or will need a left ventricular assist device or transplantation) (ACC/AHA/ESC/EACTS Stage D heart failure) 17. Deep vein thrombosis (DVT) or pulmonary embolism (PE) in the last 6 months (180 days) † 18. Stroke within the last 90 days† Note: Documented clinical diagnosis of stroke (excluding TIA) 19. Modified Rankin Scale ≥ 4 disability 20. Severe renal insufficiency with estimated glomerular filtration rate (eGFR) ≤ 25 mL/min/1.73m^2 or requiring chronic renal replacement therapy 21. Patients with hepatic insufficiency or cirrhosis with Child-Pugh score class C 22. Patient is oxygen-dependent or requires continuous home oxygen 23. Chronic anemia with transfusion dependency or Hgb < 9 g/dL not corrected by transfusion 24. Unable to walk at least 100 meters in a 6-minute walk test 25. Thrombocytopenia (Platelet count < 75,000/mm^3) or thrombocytosis (Platelet count > 750,000/mm^3) 26. Known bleeding or clotting disorders or patient refuses blood transfusion 27. Active gastrointestinal (GI) bleeding within the last 90 days† 28. Pregnant, breastfeeding, or planning pregnancy within the next 12 months (365 days) † Note: Female patients of childbearing potential need to have a negative pregnancy test performed within 14 days prior to intervention and be adherent to an accepted method of contraception 29. Patients in whom (any of the following): (a) transesophageal echocardiography is contraindicated or cannot be completed (b) tricuspid valve anatomy is not evaluable by TTE or TEE 30. In the opinion of the investigator, access to and through the femoral vein/IVC with a guide sheath and delivery catheter is deemed not feasible (e.g. occluded femoral veins, occluded or thrombosed IVC filter) 31. Untreatable hypersensitivity or contraindication to any of the following: all antiplatelets, all

Item	Details
Exclusion Criteria (Continued)	anticoagulants, nitinol alloys (nickel and titanium), bovine tissue, glutaraldehyde, or contrast media Note: Patient must be able to tolerate at least one antiplatelet medication AND one anticoagulant medication 32. Currently participating in another investigational biologic, drug or device study 33. Co-morbid condition(s) that, in the opinion of the Investigator, limit life expectancy to < 12 months (365 days) † 34. Presence of infiltrative cardiomyopathy or valvulopathy (including carcinoid, amyloidosis, sarcoidosis, hemochromatosis) or significant uncorrected congenital heart disease including but not limited to hemodynamically significant atrial septal defect, RV dysplasia, and arrhythmogenic RV Note: "Hemodynamically significant ASD" includes, but is not limited to, significant iatrogenic interatrial shunt (Qp/Qs > 1.5), persistent/pancyclic (or respirophasic) right-to-left shunt, right-to-left shunt with resting desaturation (SpO_2 < 90%). 35. Any condition, in the opinion of the investigator, making it unlikely the patient will be able to complete all protocol procedures and follow-ups 36. Other medical, social, or psychological conditions that preclude appropriate consent and follow-up, including patients under guardianship 37. Any patient considered to be vulnerable Note: A vulnerable patient is an individual who is unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response (ISO 14155) †, The reference timepoint is the date of central screening committee determination of eligibility
[redacted]	[redacted]

Item	Details
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]





[redacted]

1 Background of the Clinical Study

1.1 History of Development

1.1.1 Clinical Background of Tricuspid Regurgitation

1.1.1.1 Clinical Course and Etiology of the Disease

This device (Investigational Device ID Code: EWJ-202) is applied to the tricuspid valve in which its function is to prevent backflow impaired and the blood flow passing through the tricuspid valve causes regurgitation in the cardiac cycle. When the tricuspid valve does not function properly, which is known as Tricuspid Regurgitation (TR), it often accompanies mitral or aortic valve disease. For TR is initially asymptomatic, conventionally it was considered less clinically significant, and usually left untreated. Hence, the tricuspid valve is commonly referred to as the "forgotten" valve. According to a report, currently moderate to severe TR affects approximately 1.6 million patients in the US, of whom only 8,000 undergo tricuspid surgery annually [1]. Patients with moderate and severe TR have a poor prognosis [2] (Figure 1.1), and especially those with severe TR usually present with signs or symptoms of right heart failure (HF), including peripheral edema and ascites [3].

TR can have many underlying etiologies, but the majority of these can be divided into two major categories, primary tricuspid regurgitation or functional tricuspid regurgitation (FTR). Primary tricuspid insufficiency results from structural damage or degeneration of any component of the tricuspid valve (leaflets, annulus, chordae tendineae, papillary muscles) due to rheumatic, endocarditis, trauma, etc. In functional TR, on the other hand, there is no degeneration of the leaflet or subvalvular apparatus, and regurgitation is often secondary to left ventricular disease or right ventricular enlargement caused by pressure overload (pulmonary hypertension) or volume overload. Regurgitation occurs when the leaflet coaptation becomes insufficient due to annular dilation or leaflet tethering.

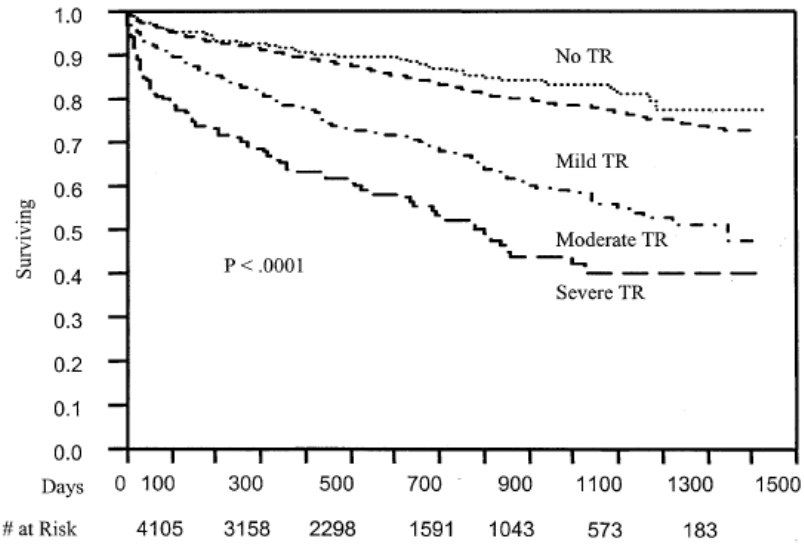


Figure1.1 Kaplan-Meier Curve in Patients with Tricuspid Regurgitation [2]

Also, in addition to these causes, recently tricuspid annular dilation originating from atrial fibrillation has been cited as a cause of functional TR [4-8]. The incidence of functional TR is higher than that of primary TR and there are reports that it accounts for approximately 80% of TR [9] and that functional TR is seen in approximately 90% of TR [10].

Significant TR may be clinically silent for a prolonged period, during which time progressive RV dilatation and dysfunction may develop, similar to changes that can occur with asymptomatic mitral regurgitation (MR) and its effect on left ventricle (LV) function.

1.1.1.2 Anatomical Characteristics and Pathophysiology of Tricuspid Valve

The tricuspid valve orifice is semilunar and consists of 3 leaflets (anterior, posterior, and septal leaflets) inserted into the fibrous annulus. Each leaflet is typically connected to a papillary muscle via chordae (in contrast, redundancy is seen in the mitral valve tissue). The tricuspid valve orifice is the largest among the cardiac valves, and the interquartile range of typical tricuspid annular diameter in Japanese has been reported to be as large as 28 to 31 mm [11]. Annular dilatation is limited to the free wall due to fixation of the annulus at the septal portion and occurs from the antero-septal junction as shown in Figure 1.1 [12].

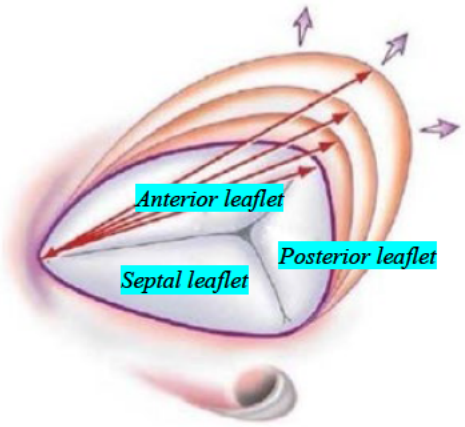


Figure 1.1 Dilatation of the Tricuspid Annulus [12]

1.1.1.3 Prognosis of Tricuspid Regurgitation

As described above, patients with TR have poor prognosis, which varies considerably depending on the severity of regurgitation [2] (Figure1.1). The above study showed that survival decreases with increasing severity of regurgitation irrespective of the left ventricular ejection fraction or pulmonary arterial pressure. Patients with severe TR have shown to have poor prognosis also in a study conducted only in patients with decreased left ventricular function [13], and similar results have also been reported in a Japanese study conducted in patients with sustained left ventricular function who have no left valvular disease [14].

1.1.1.4 Diagnosis of Tricuspid Regurgitation

TR may often be asymptomatic, and may be unexpectedly detected by echocardiography. Holosystolic heart murmur, which is typically associated with TR, can be detected by auscultation, and increases during inspiration[15]. Severe TR (typically accompanied by right heart failure) is generally associated with symptoms including jugular venous distention, lower extremities edema, ascites, fatigue, and dyspnea.

Transthoracic echocardiography (TTE) is a standard diagnostic modality for diagnosis and severity evaluation of TR[3]. Transesophageal echocardiography (TEE) is considered in specific patients for whom TTE imaging is suboptimal or who have endocarditis or a pacemaker lead, etc TTE[3]. In addition, real-time 3D echocardiography may improve evaluation and quantification of valve conditions[16]. Although cardiovascular magnetic resonance imaging (CMR) is not yet widely available, it allows more accurate evaluation of regurgitation and measurement of right ventricular function. Computed tomography (CT) is useful for measurement of the annulus and visualization of surrounding structures, and is increasingly used to appropriately plan transcatheter procedures [17].

Current severity classification of chronic TR by the American Society of Echocardiography is shown in Table 1.1 [18]. In Japan, as described in the Guidelines for the Management of Valvular Disease, it is recommended that evaluation of the severity of TR be performed according to the guidelines for evaluation of valvular disease issued by the American Echocardiography Society [19]. This severity evaluation includes qualitative, semi-quantitative, and quantitative echocardiographic parameters. Those with essentially high positive predictive value in terms of severity are shown in bold.

In addition to the criteria [18,19] presented by the American Society of Echocardiography or Japanese guidelines, the criteria [20,21]. In recent years, these criteria have frequently been used in clinical studies of transcatheter therapies, [22-24], and studies using novel severity classification of TR have been conducted including cohort studies using stratification of severe group into massive [25] and torrential [26] subgroups and a study on right ventricular remodeling [11]. In light of this background, the above endpoint was selected in the current clinical study to evaluate improvement in the severity of regurgitation more precisely.

Table 1.1 Grading the Severity of Chronic Tricuspid Regurgitation [18]

Parameter	Mild	Moderate	Severe
Structural evaluation			
TV morphology	**Normal or mildly abnormal leaflets**	Moderately abnormal leaflets	**Severe valve lesions** (e.g., flail leaflet, retraction, large perforation)
RV and RA size	Usually normal	Normal or mild dilatation	Usually dilated*
Inferior vena cava diameter	Normal <2 cm	Normal or mildly dilated 2.1-2.5 cm	dilated >2.5 cm
Qualitative Doppler			
Color Doppler jet area†	**Small, narrow, central**	Moderate central	**Large central jet** or eccentric wall-impinging jet of various size
Flow convergence	**Difficult to detect, temporarily detectable but small**	Intermediate in size and duration	**Large throughout systole**
Continuous wave Doppler waveform	**Faint/partial**/parabolic	Dense, parabolic or triangular	Dark, often triangular
Semi-quantitative			
Color Doppler jet area (cm^2)†	Not defined	Not defined	**>10**
Vena contracta width (cm)†	<0.3	0.3-0.69	**≥0.7**
PISA radius (cm)‡	≤0.5	0.6-0.9	**>0.9**
Hepatic vein flow§	Systolic dominance	Systolic blunting	**Systolic flow reversal**
Tricuspid inflow§	**A-wave dominant**	Variable	E-wave >1.0 m/sec
Quantitative			
EROA(cm^2)	<0.20	0.20-0.39‖	**≥0.40**
RVol (2D PISA) (mL)	<30	30-44‖	≥45

* RV and RA size can be within the ''normal'' range in patients with acute severe TR.
†With Nyquist limit >50-70 cm/sec
‡With baseline Nyquist limit shift of 28 cm/sec
§ Signs are nonspecific and are influenced by many other factors (RV diastolic function, atrial fibrillation, RA pressure).
‖ There are little data to support further separation of these values

Table 1.2 Expanded 5-grade Scale for Determining Severity of Tricuspid Regurgitation[20,21]

	Mild	Moderate	Severe	Massive	Torrential
Vena contracta (biplane)	<3 mm	3-6.9 mm	7-13 mm	14-20 mm	≥21 mm
EROA(PISA)	<20 mm^2	20-39 mm^2	40-59 mm^2	60-79 mm^2	≥80 mm^2
3D vena contracta area (VCA) or quantitative EROA*	-	-	75-94 mm^2	95-114 mm^2	≥115 mm^2

* 3D VCA and quantitative Doppler EROA may be larger than that for PISA EROA.

1.1.2 Current Treatments and Therapies for Tricuspid Regurgitation

1.1.2.1 Medical Treatment

In patients with severe TR, symptoms and signs of right heart failure including peripheral edema and ascites are often observed, and diuretics are mainly recommended as medical treatment for control of volume overload in ACC/AHA guidelines (Class IIa[a]) [3]. For patients with functional TR, treatment for the primary cause of heart failure (e.g., pulmonary vasodilators for increased pulmonary arterial pressure, guideline-based medical therapy [GDMT] for decreased left ventricular function, and treatment for atrial fibrillation) has been considered useful and recommended as Class IIa indication [3]. Although the European guidelines for management of valvular disease (2017 ESC/EACTS Guidelines [27]) do not provide specific descriptions related to medical treatment, when considering the ACC/AHA guidelines, basic concept of medical treatment for patients with TR is assumed to be similar. TR patients are medically managed for symptoms and typically considered as surgery candidates only after advanced RV dysfunction, liver dysfunction, and/or cirrhosis have developed.

In Japan, the medical treatment policy for TR is the same as in the US, and it is recommended to prioritize medical treatment before considering invasive treatment [19]. If symptoms of right ventricular failure persist despite medical treatment, invasive surgical treatment may be considered. Diuretics are mainly used for symptoms of right ventricular failure such as lower leg edema, and loop diuretics are frequently used. However, if sufficient effect cannot be obtained, the use of vasopressin V2 receptor antagonist (generic name: tolvaptan) is considered, and the effect of this drug on intravascular volume contraction in patients with heart failure has been confirmed in Japanese studies [28]. Since medical treatment to reduce pulmonary arterial pressure and pulmonary vascular resistance is effective for improving TR, medical treatment for pulmonary hypertension will be performed based on the guidelines [29]. If TR is caused by left-sided heart disease, surgical treatment or maximum medical treatment depending on the disease condition will be performed [30]. These treatment guidelines are essentially the same in the US and Japan, with no notable differences observed.

1.1.2.2 Surgical Intervention of the Tricuspid Valve

The decision to surgically treat TR has been controversial over the years, and surgical treatment is currently recommended for symptomatic patients and in some cases for asymptomatic patients as prophylactic treatment at the time of left-sided valve surgery[31]. The indications for surgery for severe primary TR and severe functional TR are described below in detail based on the guidelines in each country[31]. The indications for surgery for severe primary TR and severe functional TR are

[a] Class I, Procedure/Treatment SHOULD be performed/administered; Class IIa, IT IS RESONABLE to perform procedure/ administer treatment; Class IIb, Procedure/Treatment MAY BE Considered.

described below in detail based on the guidelines in each country.

(1) Indication for Surgery for Severe Primary Tricuspid Regurgitation

The ACC/AHA guidelines recommend surgery as Class IIa indication for patients with symptomatic (right heart failure) severe primary TR, whether or not it is conducted simultaneously with left heart surgeryACC/AHA.[3] On the other hand, the ESC/EACTS guidelines recommend left-sided valve surgery with simultaneous tricuspid valve surgery as well as tricuspid valve repair in patients who do not require left-sided valve surgery and have apparent symptoms as Class I indication.[27] In Japan, the Guidelines for the Management of Valvular Heart Disease published by the Japanese Circulation Society in March 2020 recommend tricuspid valve repair (or tricuspid valve replacement, if impossible) for left-sided valve surgery as Class I in patients with severe primary TR.[19] In addition, for severe primary TR with repeated symptoms of right heart failure despite medical treatment, tricuspid valve repair is recommended as Class I even if left-sided valve surgery is not performed.[19]

Therefore, there is no marked difference in the indications for surgery for severe primary TR between Japan, the US, and Europe.

(2) Indication for Surgery for Severe Functional Tricuspid Regurgitation

As in the case of primary TR, surgical treatment for severe TR is recommended as Class I indication if left-sided heart surgery is conducted.[3] In addition, since patients with symptomatic severe functional TR associated with right heart failure respond poorly to medical treatment, surgery is recommended as Class IIa indication in such patients if enlargement of the annulus is observed even in the absence of increased pulmonary arterial pressure or left-sided heart disease. TR treatment, surgical repair/replacement is uncommonly performed probably due to high morbidity and mortality related to TV surgery, especially in patients who already had previous cardiac surgery.[3,31] Most surgeons prefer to repair the TV rather than replace it, especially in functional TR.[27]

The ESC/EACTS guidelines recommend tricuspid valve surgery in patients with severe functional TR planning to undergo left-sided valve surgery as Class I indication, and surgery in patients with severe functional TR with symptomatic or progressive right ventricular enlargement/dysfunction without severe right/left ventricular dysfunction or pulmonary hypertension who have undergone left-sided heart surgery (i.e., with acceptable left-sided valve function) as Class IIa indication. [27]

In the Japanese guidelines, tricuspid valve repair performed concurrently with left-sided valve surgery is recommended as Class I for patients with severe functional TR.[19] Meanwhile, there have been recent issues of TR secondary to surgery for mitral valve disease, etc. and TR in elderly patients with atrial fibrillation, which will be addressed in the 2020 Guidelines for the Management of Valvular Heart Disease. Since patients with severe TR after cardiac surgery usually respond to medical treatment, medical treatment is performed first. However, in cases of repeated right heart failure without severe right heart dysfunction, irreversible severe pulmonary hypertension or hepatic

dysfunction, surgical intervention for tricuspid valve is recommended as Class IIa.[19] Because of the high risk of reoperation, consideration should be given to right heart function, pulmonary hypertension, and hepatic function. After risk/benefit assessment, medical treatment may be continued in some cases.[19] Treatment approach for TR with atrial fibrillation in elderly patients is similar to that for functional TR after cardiac surgery: medical treatment is first attempted and surgical intervention is considered in the case of poor treatment response with repeated right heart failure.

According to the guidelines in Japan, the US, and Europe, any surgery for severe TR performed concurrently with left-sided heart surgery is recommended as Class I. Generally, surgery is recommended as Class IIa in patients with annular dilation despite medical treatment or patients with decreased right heart function without pulmonary hypertension, although there are slight differences in expression. In conclusion, the strategy of surgical treatment for severe TR is similar, and it is considered that there is no noteworthy difference.

As mentioned in Section 1.1.1.1"Clinical Course and Etiology of the Disease", TR is mainly functional, and tricuspid valve repair is often chosen for surgical interventions for functional TR. The pathology of functional TR includes a flattening of the three-dimensional structure of the tricuspid annulus,[33,34] enlargement toward the free wall,[12,33,35] and leaflet tethering associated with right ventricular enlargement.[36, 37] Suture annuloplasty, such as the Kay repair [38], and the De Vega technique [39], has been used in the past as a technique to plicate the tricuspid annulus to repair them morphologically and reduce regurgitation. However, because of recurrence of TR,[40] ring annuloplasty has been the mainstream in recent years.

1.1.2.3 Transcatheter Treatment

Medical treatment, mainly diuretics, has been used to control heart failure and to relieve symptoms, and is not a radical treatment for TR. On the other hand, surgery which is considered as a radical treatment is not performed aggressively. According to the statistics of cardiac surgery by the Japanese Association for Thoracic Surgery, of the total 19,820 cases of surgery for acquired valvular heart disease, tricuspid valve surgery was reported in 5,512 cases, isolated tricuspid valve repair in 240 cases, and isolated tricuspid valve replacement in only 63 cases.[41] Thus, the development to realize catheter-based tricuspid valve repair or replacement has been undertaken worldwide as an alternative to low-performing surgery.[42, 43] For mitral valve position, MitraClip has already been approved as a catheter therapeutic device for degenerative and functional mitral regurgitation in Japan and abroad, and clinical experience has been accumulated. From this flow, there is an increasing interest in catheter treatment for TR, and various devices have been developed. However, many devices used for transcatheter treatment of tricuspid valve position are still under development or clinical trials,[1,23,24,44] currently, approved devices are very limited in Japan and overseas. Currently,

there are very few devices approved worldwide. The Cardioband Tricuspid Valve Reconstruction System (Edwards Lifesciences, LLC [formerly Valtech Cardio LTD, Or Yehuda, Israel]) received CE mark in April 2018 as a device for transcatheter valve annuloplasty and TriClip (Abbott Vascular) and PASCAL as a device for leaflet coaptation failure in April 2019 and May 2020, respectively. These devices have not been approved in Japan.

Meanwhile, on transcatheter tricuspid valve replacement (TTVR), there have been only case reports and retrospective studies in which SAPIEN (Edwards Lifesciences) [45-47] and Melody (Medtronic) [48] were used for valve-in-valve procedure or in patients with rheumatic disease. Due to the unique anatomy of the tricuspid valve, there have been limited reports on application to the native valve, and various devices are currently being developed by several companies.[22, 49-51] EWJ-202 has approved as a TTVR device in EU in October 2023 and in US in February 2024, respectively.

1.1.3 Positioning of EWJ-202

This device is positioned as a device to reduce or eliminate tricuspid regurgitation in patients with severe or greater tricuspid regurgitation despite medical therapy. This device, which is expected to reduce TR and improve heart failure symptoms, etc. in patients for whom other treatment options are limited, is considered to have great clinical significance.

1.1.4 Development history of EWJ-202

[redacted]

[redacted]

EWJ-202 is a transcatheter tricuspid valve replacement system characterized by the following. [redacted]

1.2 Validity of the Trial Conduct

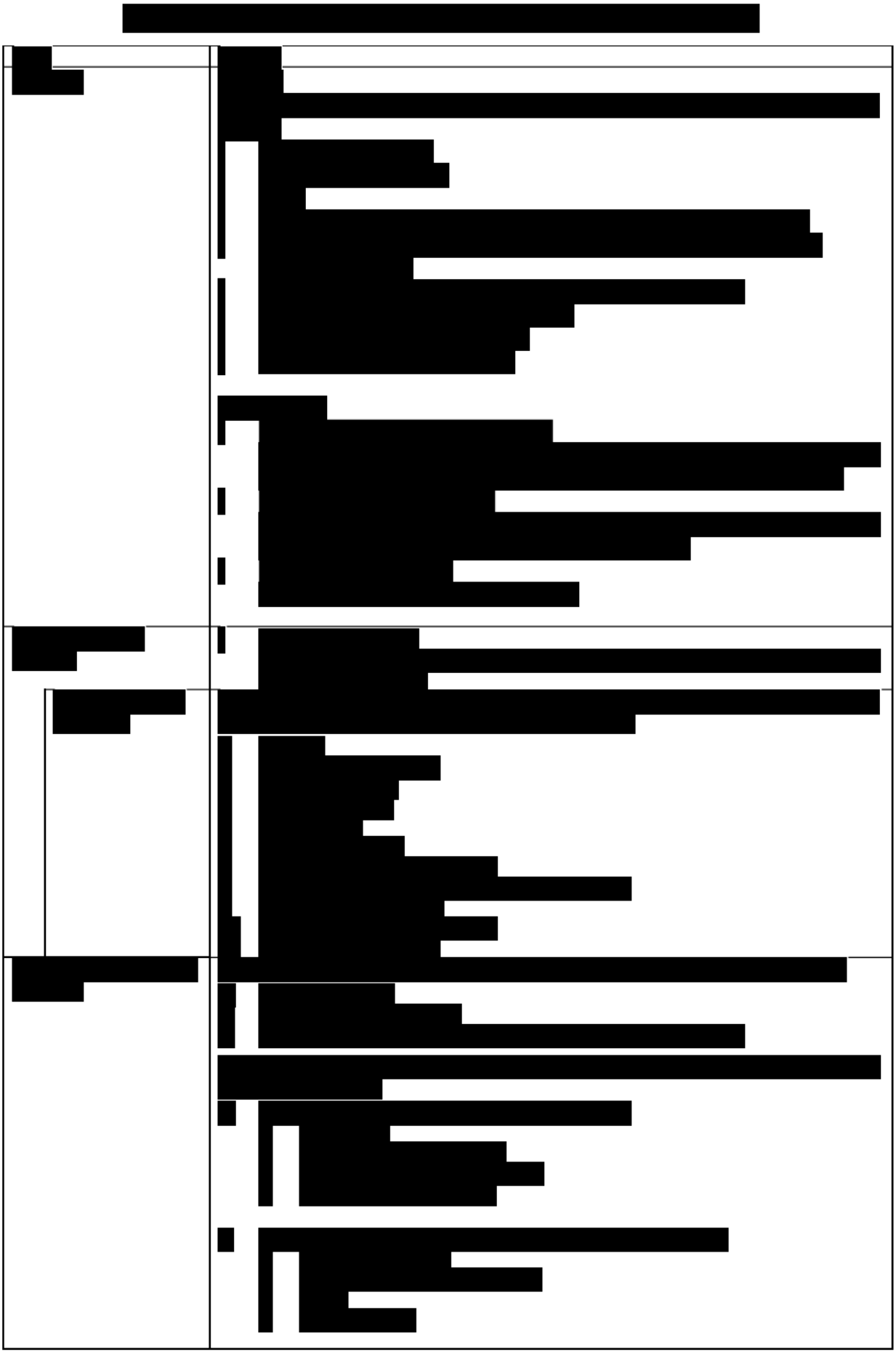
1.2.1 Nonclinical Data [redacted]

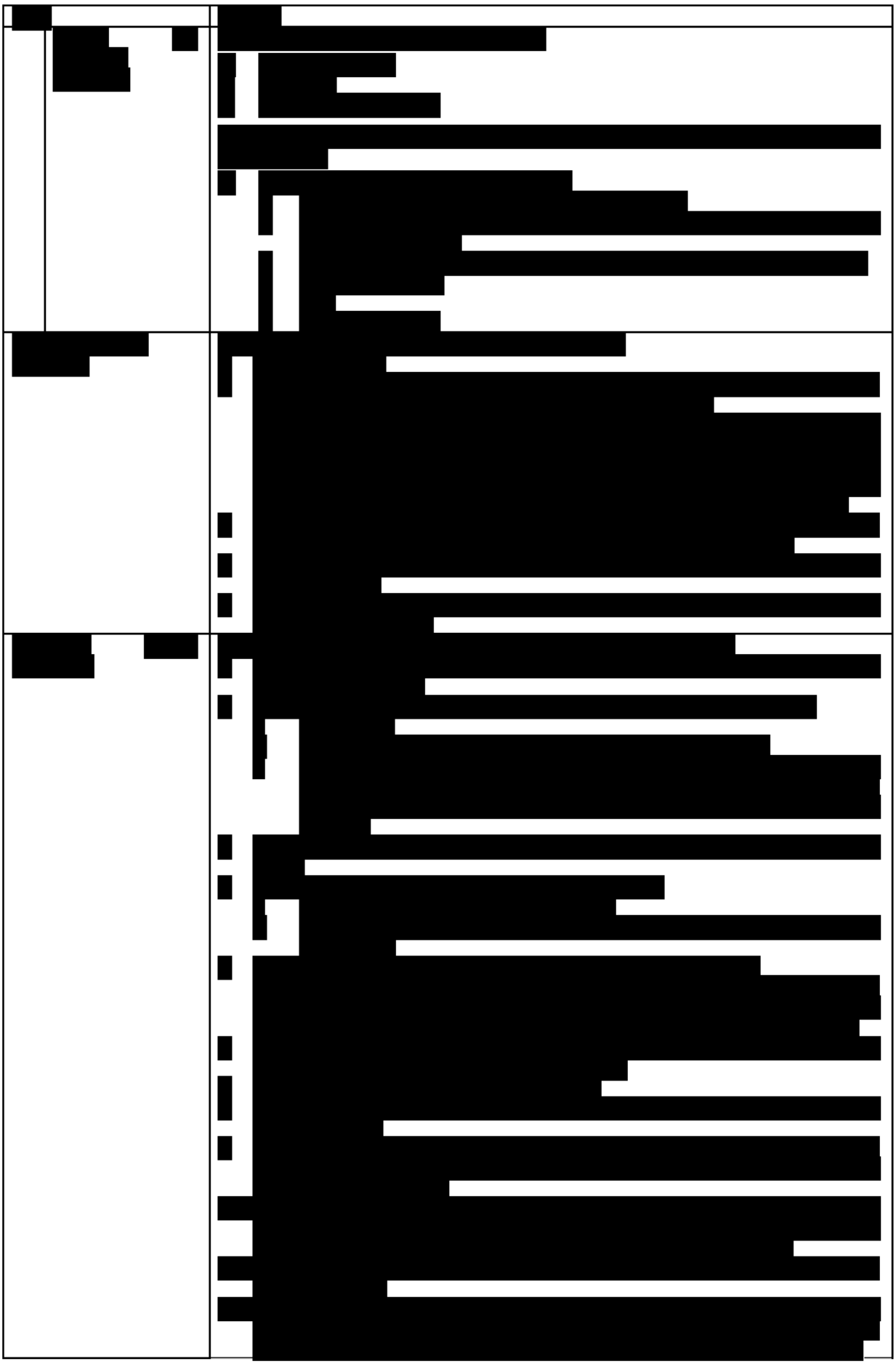
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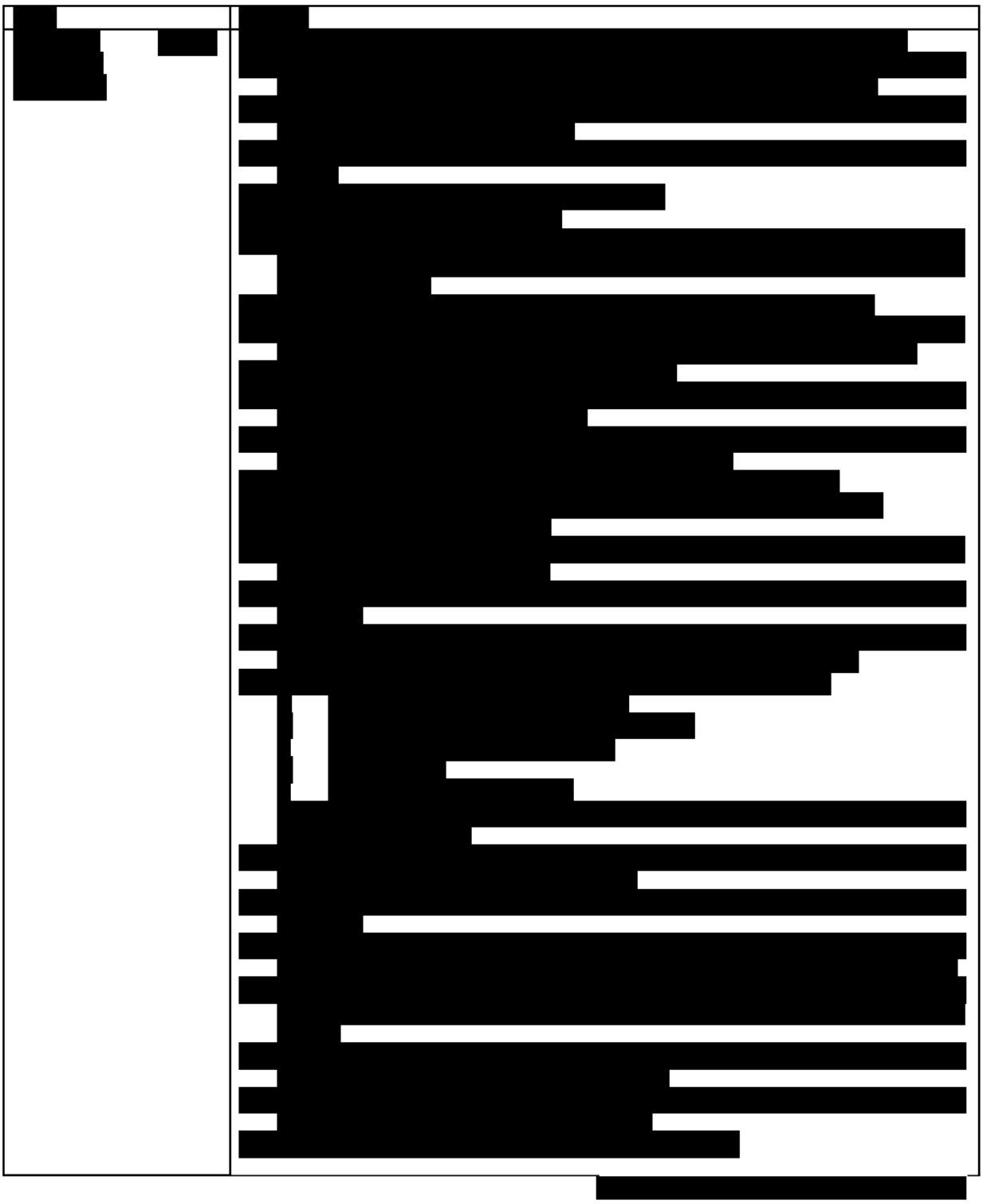
1.2.2 Results of the Preceding Clinical Studies

[redacted]

[redacted]







[redacted]

[redacted]

1.2.3 Justification for the Clinical Trial

Patients with primary or functional tricuspid regurgitation are often clinically asymptomatic despite the presence of regurgitation caused by leaflet coaptation failure. However, severe regurgitation may lead to signs such as peripheral edema and ascites, progressive right ventricular enlargement, and in some cases right ventricular dysfunction. Therefore, it is considered desirable to apply treatment promptly, before the exacerbation of heart failure symptoms, while closely monitoring the state of tricuspid valve regurgitation. The therapeutic strategy for this disease is as follows: Medical treatment is applied initially, then surgical intervention is considered if right heart failure reoccurs, with consideration for right heart function, pulmonary hypertension, and liver function in patients undergoing reoperation as they are at higher risk.[19] Medical treatment is used as symptomatic treatment and is not regarded as a radical treatment oftricuspid regurgitation. As a result, the prognosis of medical treatment is not favorable in Japan and the US.[2, 13, 14] On the other hand, surgery which is considered as a radical treatment is not performed aggressively, and it has been reported that only about 16% of patients undergo surgery after 5 years of diagnosis.[67]

Transcatheter treatment of tricuspid regurgitation is expected to improve the prognosis that cannot be achieved by medical conservative treatment and to reduce some of the risks associated with surgery in cases where surgical operation is considered. As described above, patients with severe tricuspid regurgitation have a poor prognosis and have not undergone sufficient surgical treatment despite the serious nature of the disease, representing the so-called unmet medical need. In recent years, various catheter-based devices have been developed for the treatment of tricuspid regurgitation to address the unmet needs that exists. This treatment is expected to be an effective catheter-based treatment for reduction or resolution of regurgitation and for the alleviation of symptoms of cardiac failure. EW has developed a catheter-based device for tricuspid valve replacement that have conventionally been performed surgically by taking advantage of interventional treatment to reduce physical stress on patients and following the technology developed with transcatheter aortic valve replacement (TAVR).

As summarized in the Clinical Investigator's Brochure, the protocol for the domestic trial has been established with comprehensive consideration for the safety and performance of EWJ-202 confirmed in non-clinical studies as well as clinical experience conducted overseas. [redacted]

It was judged appropriate to conduct this trial also in Japan with consideration for the potential risk and benefit balance associated with the use of EWJ-202.

2 Trial Organization

2.1 Investigational Sites

[redacted]

2.2 Sponsor

[redacted]

2.3 Contract Research Organization

[redacted]

3 Investigational Device Overview

3.1 Device Characteristics and Components

Kind of Investigational Device (Generic name): Transcatheter tricuspid valve replacement system (Plan)

The investigational device EWJ-202 is designed for transcatheter treatment of TR in patients with at least severe TR despite medical treatment.

[redacted]

Table 3.1 EWJ-202 Components and accessories with model number

[redacted]

(1) Bioprosthetic valve

[redacted]



[redacted]

(2) Delivery System

[redacted]

[redacted]

(3) Dilator Kit

[redacted]

(4) Loading System

[redacted]

(5) Accessories: Stabilizer, Base, and Plate

[redacted]



[redacted]

3.2 Usage Method

[redacted]

4 Risks and Benefits

4.1 Potential benefits

[redacted]

4.2 Potential risks

The risk management process in accordance with EN/ISO 14971:2012 was implemented. The risk management plan was also developed to perform risk analysis.

The risk analysis confirmed that the residual risks associated with EWJ-202 were similar to the clinical risks associated with other catheter-based (transcatheter) valve replacement systems and could be reduced to an acceptable level. Table 4.1 presents anticipated or potential adverse events in patients participating in clinical studies of EWJ-202. Complications may occur at any time during the procedure, post-procedure or follow-up period.

These events may be associated with the EWJ-202, transcatheter procedure, diagnostic cardiac tests (e.g. TEE, TTE, MSCT scan, etc.), ancillary procedures or may occur in the heart failure population over time. The following anticipated AEs have been identified as possible complications of the EVOQUE System and procedure:

Table 4.1 Anticipated or potential Adverse Events

- Abnormal lab values
- Allergic reaction to anesthesia, contrast media, anti-coagulation medication or device materials
- Anaphylactic shock
- Anemia or decreased Hgb, may require transfusion
- Aneurysm or pseudoaneurysm
- Angina or chest pain
- Arrhythmia – atrial (i.e. AF, SVT)
- Arrhythmias – ventricular (i.e. VT, VF)
- Arterio-venous fistula
- Bleeding
- Cardiac (heart) failure
- Cardiac arrest
- Cardiac injury, including perforation
- Cardiac tamponade / pericardial effusion
- Cardiogenic shock
- Chordal entanglement or rupture that may require intervention
- Coagulopathy, coagulation disorder, bleeding diathesis
- Conduction system Injury, which may require implantation of a pacemaker (temporary or permanent)
- Conversion to open heart surgery
- Coronary artery occlusion
- Damage to or interference with function of pacemaker or implantable cardioverter defibrillator (ICD)
- Death
- Edema
- Electrolyte imbalance
- Embolization including air, particulate, calcific material, or thrombus
- Emergent cardiac surgery
- Endocarditis
- Esophageal irritation
- Esophageal perforation or stricture
- EWJ-202 component(s) embolization
- Failure to retrieve any EWJ-202 components
- Fever
- Gastrointestinal bleeding
- Hematoma
- Hemodynamic compromise
- Hemolysis / hemolytic anemia
- Hemorrhage requiring transfusion/surgery
- Hypertension
- Hypotension
- Inflammation
- Injury to the tricuspid apparatus including chordal damage, rupture, papillary muscle damage
- Leaflet tearing
- Local and systemic infection
- Mesenteric ischemia or bowel Infarction
- Multi-system organ failure
- Myocardial infarction
- Nausea and/or vomiting
- Nerve injury
- Neurological symptoms, including dyskinesia, without diagnosis of TIA or stroke
- Non-emergent reoperation
- Pain
- Pannus formation
- Paralysis
- Percutaneous valve intervention
- Peripheral ischemia
- Permanent disability
- Pleural effusion
- Pneumonia
- Pulmonary edema
- Pulmonary embolism
- Reaction to anti-platelet or anticoagulation agents
- Rehospitalization
- Renal failure
- Respiratory failure, atelectasis – may require prolonged intubation
- Retroperitoneal bleed
- RVOT obstruction
- Septicemia, sepsis
- Skin burn, injury or tissue changes due to exposure to ionizing radiation
- Stroke
- Structural deterioration (wear, fracture, calcification, leaflet thickening, stenosis of implanted study device, or new leaflet motion disorder)
- Thromboembolism
- Transient ischemic attack (TIA)
- Valve dislodgement/Embolization
- Valve endocarditis
- Valve explant
- Valve leaflet entrapment
- Valve malposition
- Valve migration
- Valve paravalvular leak (PVL)
- Valve regurgitation (new or worsening tricuspid, aortic, mitral, pulmonary)
- Valve stenosis
- Valve thrombosis
- Vascular injury or trauma, including dissection or occlusion
- Vessel spasm
- Wound dehiscence, delayed or incomplete healing

There may also be other risks that are unknown at this time. Adverse events will be collected and reviewed throughout the duration of the study and follow-up period. The Investigators will be notified of any additional risks identified that could affect the health, safety or welfare of the study patients.

4.3 Risk management

All efforts will be made to minimize the identified risks by taking the following measures:

- Selection of investigators in this trial: Interventional Cardiologist or Cardiothoracic Surgeon must be board certified (or equivalent), experienced with performing transcatheter heart valve repair and replacement, and skilled in percutaneous coronary interventions and structural heart interventions as well as access site management.
- Sponsor develops well-defined clinical study protocol, including specific inclusion/exclusion criteria to enroll appropriate patients in the study, and trains principal investigator, sub-investigator(s), and clinical research coordinator(s). (See 9.1.1 "Protocol Training")
- Investigators will be trained in proper procedure performance and device operation prior to patient treatments. (See 9.1.2 "Training on Investigational Device and Procedure")
- Central Screening Committee ensures appropriate and consistent patient selection across study sites.
- During the procedure, the Clinical Specialist of the sponsor will attend all cases to respond to any questions regarding the device and/or the procedure, in order to ensure the safety of the patients.
- Close patient monitoring during the implant procedure and follow-up period.
- Ongoing monitoring of study data and results, including the use of independent Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB)

5 Objective

The objective of this trial is to cofirm the safety and effectiveness of EWJ-202 under the healthcare environment in Japan in patients with at least severe tricuspid regurgitation despite medical therapy.

6 Safety and Effectiveness

6.1 Primary endpoint (Co-primary)

[Primary Safety and Effectiveness Endpoint]
All-cause mortality (1-year post procedure) Heart failure hospitalization (1-year post procedure)

<Rationale>

EWJ-202 is a device to perform transcatheter replacement of tricuspid valve in patients with at least severe TR despite medical treatment. It is positioned as a device for transcatheter treatment that is expected to improve the prognosis of patients by reducing or eliminating tricuspid regurgitation as well as to reduce the physical burden on patients compared to highly invasive surgical procedures.

The two co-primary endpoints, all-cause mortality and heart failure hospitalization were set as the primary endpoint of this trial for investigation of prognosis improvement.

In severe or greater TR, which is the target disease of this trial, medical treatment is preferentially administered to relieve symptoms. However, its prognosis is poor,[2,13,14] and it is not a curative treatment for TR. On the other hand, surgical treatment, especially isolated tricuspid valve surgery, is not actively performed, and hospital mortality is relatively high, at 4.6% and 6.3% for tricuspid valve repair and tricuspid valve replacement, respectively. [41]. In view of this situation in Japan, the existing treatment for severe TR regards as medical therapy, and we hoped that this device would improve the prognosis of patients with severe TR (improvement of life expectancy with TR reduction or resolved), which has not been achieved by medical therapy.
Therefore, judged that it was appropriate to set two co-primary endpoints, all-cause mortality and heart failure hospitalization as the primary endpoint of this Japan trial.

For the definition of heart failure hospitalization, see Section 28 "Definition of Terms."

6.2 Secondary endpoints

<Effectiveness endpoint>

(1) TR grade (30 days, 6 months, 1 year, and annually until 5 years)

(2) NYHA Classification (30 days, 6 months, 1 year, and annually until 5 years)

(3) QOL (30 days, 6 months, 1 year,2 years)
- SF-36
- KCCQ
- EQ-5D-5L

(4) 6MWD (30 days, 6 months, 1 year,2 years)

<Safety endpoint>

(1) Composite endpoint of Major Adverse Events (MAE) (30 days)
- Cardiovascular mortality
- Myocardial infarction
- Stroke
- New need for renal therapy
- Severe bleeding*
- Non-elective tricuspid valve re-intervention (percutaneous or surgical)
- Major† access site and vascular complications
- Major‡ cardiac structural complications due to access-related issues
- Device-related pulmonary embolism
- Arrhythmia and conduction disorder requiring permanent pacing

(2) Individual components of MAE (30 days, 6 months, 1 year, and annually until 5 years)

(3) All-cause mortality (30 days, 6 months, 1 year, and annually until 5 years)

(4) Number of heart failure hospitalizations (30 days, 6 months, 1 year, and annually until 5 years)

(5) All-cause hospitalizations (30 days, 6 months, 1 year, and annually until 5 years)

(6) Durable right ventricular assist device (RVAD) implantation or heart transplant (30 days, 6 months, 1 year, and annually until 5 years)

(7) Tricuspid valve surgery or percutaneous tricuspid intervention (30 days, 6 months, 1 year, and annually until 5 years)

(8) Need for paracentesis (30 days, 6 months, 1 year, and annually until 5 years)

*, Fatal, life-threatening, extensive, or major bleeding as defined by MVARC.[60]
†, "Major" as defined by MVARC.[60]
‡, "Major" as defined by MVARC.[60]Cardiac perforation (including the left ventricle, left atrium, coronary sinus, right atrium, and right ventricle) or pseudoaneurysm resulting in death, life-threatening bleeding, hemodynamic compromise, or tamponade, or requiring unplanned surgical or percutaneous intervention

See also Section 28 "Definition of Terms."

6.3 Exploratory Endpoints

[redacted]

[redacted]

Each exploratory endpoint is defined below.

[redacted]

[redacted]

6.4 Additional outcomes

[redacted]



[redacted]

7 Clinical Trial Design

7.1 Clinical Trial Design

Prospective, open, non-randomized, multicenter, clinical trial

<Rationale>

The EWJ-202 is a catheter-based tricuspid valve replacement device for patients with at least severe tricuspid regurgitation despite medical therapy. In addition to reducing the physical burden on patients compared to highly invasive surgical procedures, catheterization with this device is expected to improve prognosis by reducing or eliminating tricuspid regurgitation. [redacted]

As described in Section 1.1, "Background of development," medical therapy for tricuspid regurgitation is not a curative treatment because it is performed as a symptomatic treatment, and the prognosis is extremely poor. Though the similar tendency is obtained in Japan, the report is scarce, and there are still many unclear points on the domestic result of the medical treatment. Randomized clinical trials are the best way to solve these problems because they can clarify the positioning of this device against existing therapies. In the meantime, the problem that the enrollment speed may be slow from the viewpoint of the acquisition of the consent is intervened from the nature of the trial design in which the treatment group is randomly allocated. Some patients are also assigned to medical treatment, which clearly has a poor prognosis. [redacted]

Therefore, this trial was designed as a prospective, open, non-randomized, multicenter clinical trial to confirm the safety and effectiveness of EWJ -202 in Japanese patients with severe or greater tricuspid regurgitation.

7.2 Planned number of subjects and the rationale

7.2.1 Main Cohort (Evaluable)

45 subjects

<Rationale>

Patients meeting all the inclusion criteria and none of the exclusion criteria will be able to participate in the primary cohort of this study after confirmation of the eligibility by the central screening committee (CSC). Before participation in the primary cohort, Roll-in of up to 3 patients per trial site must be completed as shown in Section 7.2.2.

The purpose of this trial is to confirm the safety and effectiveness of this device [redacted]. In this Japan trial, the primary endpoint was the two co-primary endpoints of all-cause mortality and heart failure (HF) hospitalization. [redacted]

All-cause mortality:

[redacted]

[redacted]

HF hospitalization:

[redacted]

[redacted]

7.2.2 Roll-in Cohort

Up to 3 subjects per site

<Rationale>

This investigational plan incorporates a roll-in cohort to provide experience in use of the EWJ-202 prior to enrolling patients into the main cohort at a given investigational site.

Roll-in patients must meet the same inclusion/exclusion criteria for the main cohort and must be confirmed as eligible by the echo core lab and the central screening committee (CSC).

The roll-in cohort will include a maximum of 3 patients per study site.

[redacted]

Whether enrollment into the primary cohort can be initiated will be determined by the sponsor in consideration of the conditions at each investigational site.

Data from Roll-in patients will be analyzed as a separate cohort (Roll-in Population) from the primary cohort, in principle. However, pooled analysis may be performed as necessary and and the results may be presented as reference information in Clinical Study Report.

7.3 Number of planned investigational sites

Up to 8 sites

<Rationale>

It was selected from the perspectives of ensuring the study quality and of the feasibility.

7.4 Planned trial period

[redacted]

7.5 Expected duration of patient participation

All the enrolled subjects will be followed up until 5 years post procedure, whether the subject is in Roll-in or primary cohort.

The assessment will be performed at baseline, at the time of the procedure, immediately after the procedure / before discharge, at discharge (or 7 days post procedure, whichever comes earlier), and at 30 days, 6 months, 1 year, and annually until 5 years post-procedure.

8 Subjects

8.1 Target population

Patients with at least severe tricuspid regurgitation

8.2 Eligibility Criteria

8.2.1 Disposition of Trial Population

Subjects of this trial will receive pre-test instructions prior to subject enrollment and provide the written consent, followed by the screening based on the inclusion / exclusion criteria. In the process of subject enrollment, the investigational site will prepare the subject enrolment log (Screening Log).

8.2.2 Inclusion Criteria

The study will include patients who meet **ALL** the following inclusion criteria from (1) to (5).

(1) Age ≥ 18 years old at the time of consent

(2) Despite medical therapy (OMT) per the Local Heart Team, patient has signs of TR (ascites, edema, etc), symptoms from TR*, or prior heart failure hospitalization from TR

Note:

Patient must be on OMT per the local heart team at the time of TR assessment for trial eligibility (TTE). Medical therapy includes stable diuretic medications, unless patient has documented history of intolerance. Oral diuretic doses must be stable (i.e. no decrease of more than ½ or increase of 2x) in the 7 days prior to the baseline/screening TTE. Efforts should be made to keep oral diuretic doses stable after the TTE.

*, include, but are not limited to, patient classification as NYHA class II, III, or IVa, shortness of breath, fatigue, abdominal swelling, indigestion due to venous congestion of the gastrointestinal tract, etc.

(3) Functional and/or degenerative TR graded as at least severe on a transthoracic echocardiogram (assessed by the echo core lab using a 5-grade classification)

(4) The Local Heart Team determines that the patient is appropriate for transcatheter tricuspid valve replacement

(5) Patient is willing and able to comply with all specified study evaluations and provides written informed consent

[redacted]

[redacted]

8.2.3 Exclusion Criteria

Patient judged to meet ANY of the following criteria (1) to (37) at screening cannot be enrolled into this trial.

(1) Anatomy precluding proper EWJ-202 delivery, deployment and/or function. (Assessed by echo core lab and/or sponsor)
(2) LVEF < 25% (Assessed by echo core lab)
(3) Evidence of severe right ventricular dysfunction (Assessed by echo core lab)
(4) Any of the following pulmonary pressure parameters (any of the following, as assessed by echo core lab, as applicable):
    (a) Pulmonary arterial systolic pressure (PASP) > 60 mmHg by echo doppler (unless right heart catheterization [RHC] demonstrates PASP ≤ 70 mmHg) (Assessed by ECL)
    (b) PASP > 70 mmHg by RHC
    (c) Pulmonary Vascular Resistance (PVR) > 5 Wood units by RHC (unless PVR ≤5 Wood units and systolic BP >85 mmHg after vasodilator challenge).
(5) Previous tricuspid surgery or intervention
(6) Presence of trans-tricuspid pacemaker or defibrillator lead with any of the following:
    (a) Implanted in the RV within the last 90 days†
    (b) Patient is pacemaker dependent [65] on trans-tricuspid lead without alternative pacing

option

(c) Has delivered appropriate ICD therapy

Note:

Patients with RV lead extraction are required to wait 30 days prior to the baseline/screening TTE

(7) Severe aortic, mitral and/or pulmonic valve stenosis and/or regurgitation. (Assessed by echo core lab)

Note:

patients with concomitant mitral or aortic or pulmonic and tricuspid valve disease will have the option of getting their respective valve treated, and wait 60 days post transcatheter or 90 days after surgical treatment prior to being reassessed for the study

(8) Active endocarditis within the last 90 days† or infection requiring antibiotic therapy (oral or intravenous) within the last 30 days†

(9) Hemodynamically significant pericardial effusion

(10) Significant intra-cardiac mass, thrombus, or vegetation (Assessed by echo core lab)

Note:

Chronic scarred LV apical or LAA thrombi can be considered.

(11) Clinically significant, untreated coronary artery disease requiring revascularization, evidence of acute coronary syndrome, recent myocardial infarction within the last 30 days†

(12) Any of the following cardiovascular procedures:

(a) Percutaneous coronary, intracardiac, or endovascular intervention within the last 30 days†

Note:

Intracardiac intervention includes, but is not limited to: left atrial appendage occlusion, ASD closure, AF ablation

(b) Carotid surgery within the last 30 days†

(c) Direct current cardioversion within the last 30 days†

(d) Leadless RV pacemaker implant within the last 30 days†

(e) Cardiac surgery within the last 90 days†

(13) Known history of untreated severe symptomatic carotid stenosis (>50% by ultrasound) or asymptomatic carotid stenosis (>70% by ultrasound)

(14) Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months (365 days) †, or any planned percutaneous cardiac procedures within the next 90 days†

(15) Hypotension (systolic pressure < 90 mmHg) or requirement for inotropic support or hemodynamic support within the last 30 days †

(16) Patient with refractory heart failure requiring advanced intervention (i.e. patient has or will need a left ventricular assist device or transplantation) (ACC/AHA/ESC/EACTS Stage D heart failure)

(17) Deep vein thrombosis (DVT) or pulmonary embolism (PE) in the last 6 months (180 days) †

(18) Stroke within the last 90 days†

Note: Documented clinical diagnosis of stroke (excluding TIA)

(19) Modified Rankin Scale ≥ 4 disability

(20) Severe renal insufficiency with estimated glomerular filtration rate (eGFR) ≤ 25 mL/min/1.73m^2 or requiring chronic renal replacement therapy

(21) Patients with hepatic insufficiency or cirrhosis with Child-Pugh score class C

(22) Patient is oxygen-dependent or requires continuous home oxygen

(23) Chronic anemia with transfusion dependency or Hgb < 9 g/dL not corrected by transfusion

(24) Unable to walk at least 100 meters in a 6-minute walk test

(25) Thrombocytopenia (Platelet count < 75,000/mm^3) or thrombocytosis (Platelet count > 750,000/mm^3)

(26) Known bleeding or clotting disorders or patient refuses blood transfusion

(27) Active gastrointestinal (GI) bleeding within the last 90 days†

(28) Pregnant, breastfeeding, or planning pregnancy within the next 12 months (365 days) †

Note: Female patients of childbearing potential need to have a negative pregnancy test performed within 14 days prior to intervention and be adherent to an accepted method of contraception

(29) Patients in whom (any of the following):

(a) transesophageal echocardiography is contraindicated or cannot be completed

(b) tricuspid valve anatomy is not evaluable by TTE or TEE

(30) In the opinion of the investigator, access to and through the femoral vein/IVC with a guide sheath and delivery catheter is deemed not feasible (e.g. occluded femoral veins, occluded or thrombosed IVC filter).

(31) Untreatable hypersensitivity or contraindication to any of the following: all antiplatelets, all anticoagulants, nitinol alloys (nickel and titanium), bovine tissue, glutaraldehyde, or contrast media

Note:

Patient must be able to tolerate at least one antiplatelet medication AND one anticoagulant medication

(32) Currently participating in another investigational biologic, drug or device study

(33) Co-morbid condition(s) that, in the opinion of the Investigator, limit life expectancy to < 12 months (365 days) †

(34) Presence of infiltrative cardiomyopathy or valvulopathy (including carcinoid, amyloidosis, sarcoidosis, hemochromatosis) or significant uncorrected congenital heart disease including but not limited to hemodynamically significant atrial septal defect, RV dysplasia, and arrhythmogenic RV

Note:

"Hemodynamically significant ASD" includes, but is not limited to, significant iatrogenic interatrial shunt (Qp/Qs > 1.5), persistent/pancyclic (or respirophasic) right-to-left shunt, right-to-left shunt with resting desaturation (SpO2 < 90%).

(35) Any condition, in the opinion of the investigator, making it unlikely the patient will be able to complete all protocol procedures and follow-ups

(36) Other medical, social, or psychological conditions that preclude appropriate consent and follow-up, including patients under guardianship

(37) Any patient considered to be vulnerable

Note:

A vulnerable patient is an individual who is unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response (ISO 14155)

†, The reference timepoint is the date of central screening committee determination of eligibility

[redacted]

[redacted]

[redacted]

[redacted]

9 Methods of the Trial

9.1 Training

9.1.1 Protocol Training

The principal investigator, subinvestigator(s), and clinical research coordinator(s) must complete the training provided by the sponsor. The training includes, but not limited to, the following contents:

- The trial protocol
- Flow of case review
- Data entry in eCRF
- Overview of the investigational device

As necessary, the sponsor may provide the training continuously as face-to-face, online, or other forms of training.

The sponsor may also provide a re-training to any investigational site with non-compliance with the protocol, etc.

The training will be documented, and the original record will be retained by the investigational site, with a copy retained by the sponsor.

9.1.2 Training on Investigational Device and Procedure

The investigator or sub-investigator(s) performing the procedure must complete the training program provided by the sponsor before enrolling any subject into the study. The training will include lectures, hands-on training, or other styles of learning so that the trainee can learn to perform the procedure and to operate the investigational device appropriately.

The training will be documented, and the training log will be retained by the sponsor.

9.2 Informed Consent

Informed consent should be obtained from the subject in compliance with the following procedure:

(1) The investigator or sub-investigator(s) will provide the subject with full and adequate information using the written information approved by the Institutional Review Board (IRB) and other appropriate materials, and obtain voluntary written consent from the subject to participate in the trial. The investigator or sub-investigator(s) should take the following points into consideration when providing the information:

- The subject should not be coerced or unduly influenced to participate in the trial
- The information should not cause the subject to waive or to appear to waive any legal rights
- None of the information should contain any language that releases or appears to release the investigator, sub-investigator(s), clinical research coordinator(s), investigational site, or sponsor from legal responsibilities
- The language used should be general and easy for the subject to understand

- Before providing the consent, the subject should be given opportunities to ask questions and ample time to decide whether or not to participate in the trial

(2) After fully understanding the contents of the trial, the subject will sign and date the informed consent form stating that the subject provides consent to participate in the trial. The investigator or sub-investigator(s) who provided study information to the subject will sign and date the subject's informed consent form. If the subject is unable to read but is able to understand the contents of written information when explained orally or by any other communication method, an impartial witness should be present. In that case, both the subject and the witness will sign the informed consent form, and the subject will record the date of consent and the witness the date of attendance. For the subject who is unable to provide a written consent because of physical or other problem, also should present an impartial witness, and the witness will sign and date the subject's informed consent form. At the same time, the investigator or sub-investigator(s) will document the fact that the subject has provided the voluntary consent to participate in the trial along with the reason why the written consent cannot be obtained from the subject.

If the clinical research coordinator has provided supplementary explanation, the clinical research coordinator will also sign and date the form.

(3) The investigator or sub-investigator(s) will provide the person to be the subject's legal representative with full and adequate information using the IRB-approved informed consent form and other appropriate materials, if considered necessary, and obtain the voluntary written consent based on the judgement as to whether the participation in the trial is appropriate in terms of the welfare and benefit of the subject.

(4) The investigator or sub-investigator(s) should not perform any trial-specific test or other procedures before obtaining the written consent. The investigator or sub-investigator(s) will inquire if the subject is being treated by any other physician, and if yes, will inform the treating physician of the subject's participation in this trial with the subject's agreement. If the investigator or sub-investigator(s) expects that the subject would visit any other hospital or department newly after participating in this trial, the investigator or sub-investigator(s) will instruct the subject to inform of the ongoing participation in a clinical trial.

(5) If obtaining new information that may be relevant to the subject's willingness to continue participation in the trial, the investigator or sub-investigator(s) should provide the subject and the subject's legal representative if the principle investigator or the sub-investigator(s) considers it necessary with the information in a timely manner and confirm whether the subject intends to continue to participate in the trial and document accordingly in the medical record, etc.

(6) The investigator will amend the written information based on the relevant information in a timely manner, if the investigator considers it necessary. The investigator will report the amendment of the written information to the head of the investigational site and obtain the approval of IRB.

After approval, the investigator or sub-investigator(s) will obtain the written consent etc. according to the procedure as provided for in the preceding paragraph from (1) to (3) from the subject again to continue participation in the trial.

(7) The investigator or sub-investigator(s) will give a copy of the signed consent form and the written information to the subject. The signed original consent form will be retained by the investigational site.

(8) The investigator or sub-investigator(s) will enter into the eCRF the date of the written consent by the subject, the date of the written consent by the witness if the witness was required, and the date of the written consent by the legal representative if the consent was obtained from the legal representative.

9.3 Case Review

The echo core lab and CSC will review the patients whose participation in the trial is being discussed. Prior to submission of the case information for case review, the investigator and Heart Team of the investigational site will perform screening of the patient based on the inclusion/exclusion criteria. Once the screening is completed and the eligibility is confirmed by the investigational site, the investigational site will submit the case information of this patient to CSC.
The patient will be able to participate in the trial if the eligibility for trial participation is approved by CSC. If not approved, the patient will be regarded as a screening failure who can neither participate in the trial nor undergo the trial procedure.

If a patient appears to be ineligible for the enrollment during screening, the patient or the legal representative, if any, should be notified accordingly.

The sponsor will document and retain the record of case review.

9.4 Subject Enrollment

9.4.1 Subject Enrollment Process

The screening and enrollment will be documented for all the patients evaluated for eligibility for trial participation.

(1) The investigator and sub-investigator(s) will provide the written information to patients who are potential candidate subjects of this trial and explain the details of the study in order to obtain the consent to participate in the trial.

(2) The investigator or sub-investigator(s) will obtain the written consent as described in Section 9.2.

(3) Patients who have provided the written consent will be assessed for the eligibility based on the inclusion/exclusion criteria. For those patients who provided the consent but did not meet the eligibility criteria, ineligible items (reasons) will be recorded in the inclusion/exclusion criteria form of EDC.

(4) After confirmation of the eligibility at each investigational site, case review will take place as described in Section 9.3 to determine whether each patient can participate in the trial. Results of the case review will be documented.

9.4.2 Definition of Subject Enrollment

Patients must sign the consent form, meet all the inclusion criteria and none of the exclusion criteria, and be accepted by CSC for participation.

The subject enrollment in this trial is defined as “having undergone the index procedure at the time when invasion such as puncture or skin incision at the access site is started for introduction of the study device.”

The subject identification code will be used for recording in the trial-related documents and for identifying the subject.

For the trial flow diagram, see Figure 9.1.

9.5 Imaging Assessment

Imaging assessment (TTE, TEE, and CT) will be performed in accordance with the latest operating procedure (manual) . If there are any images or views available that are required for assessment of the anatomical inclusion / exclusion criteria and for evaluation of TR grade, the existing images taken in routine medical care may be used for evaluation at screening / baseline. [redacted].

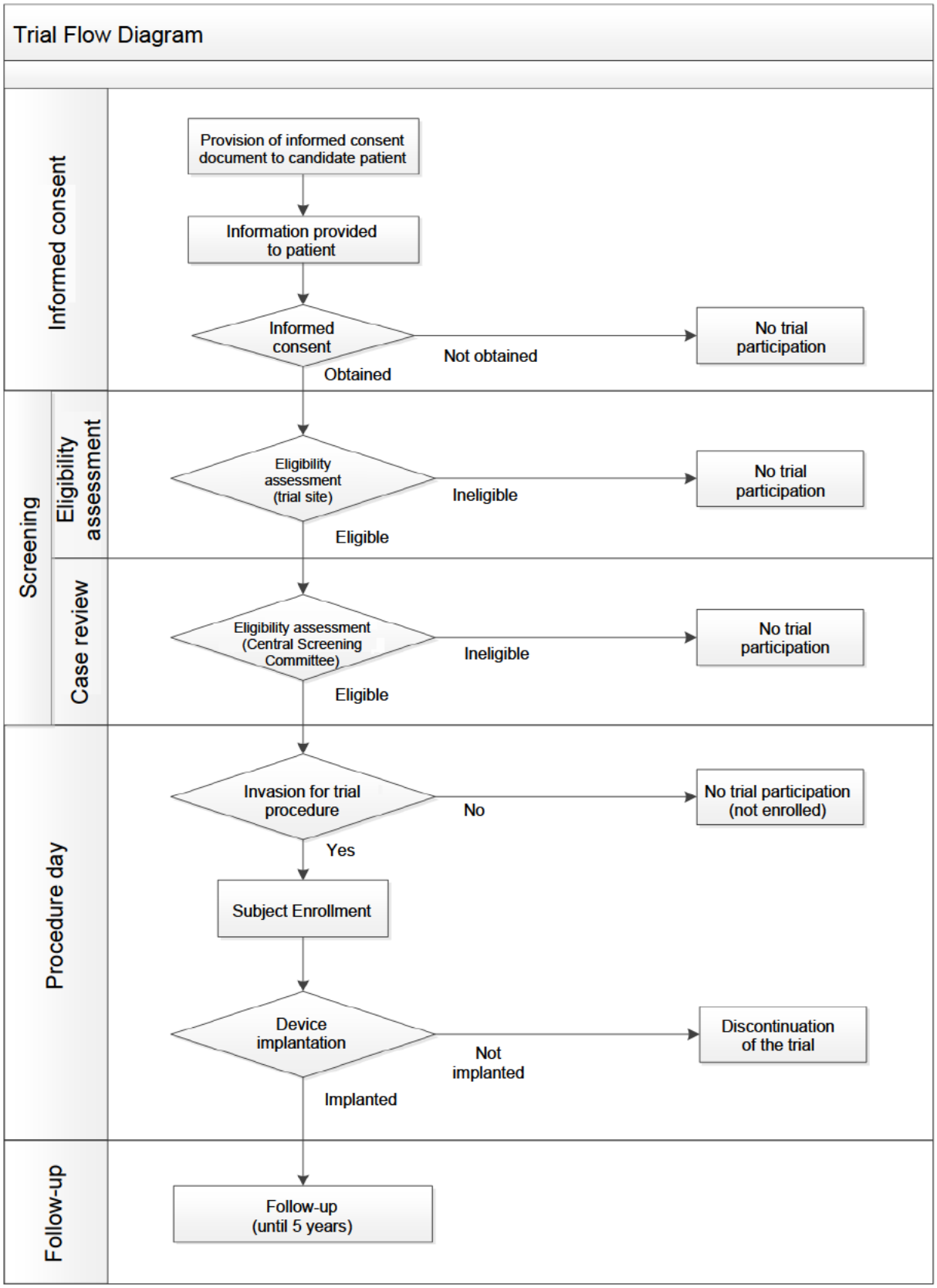
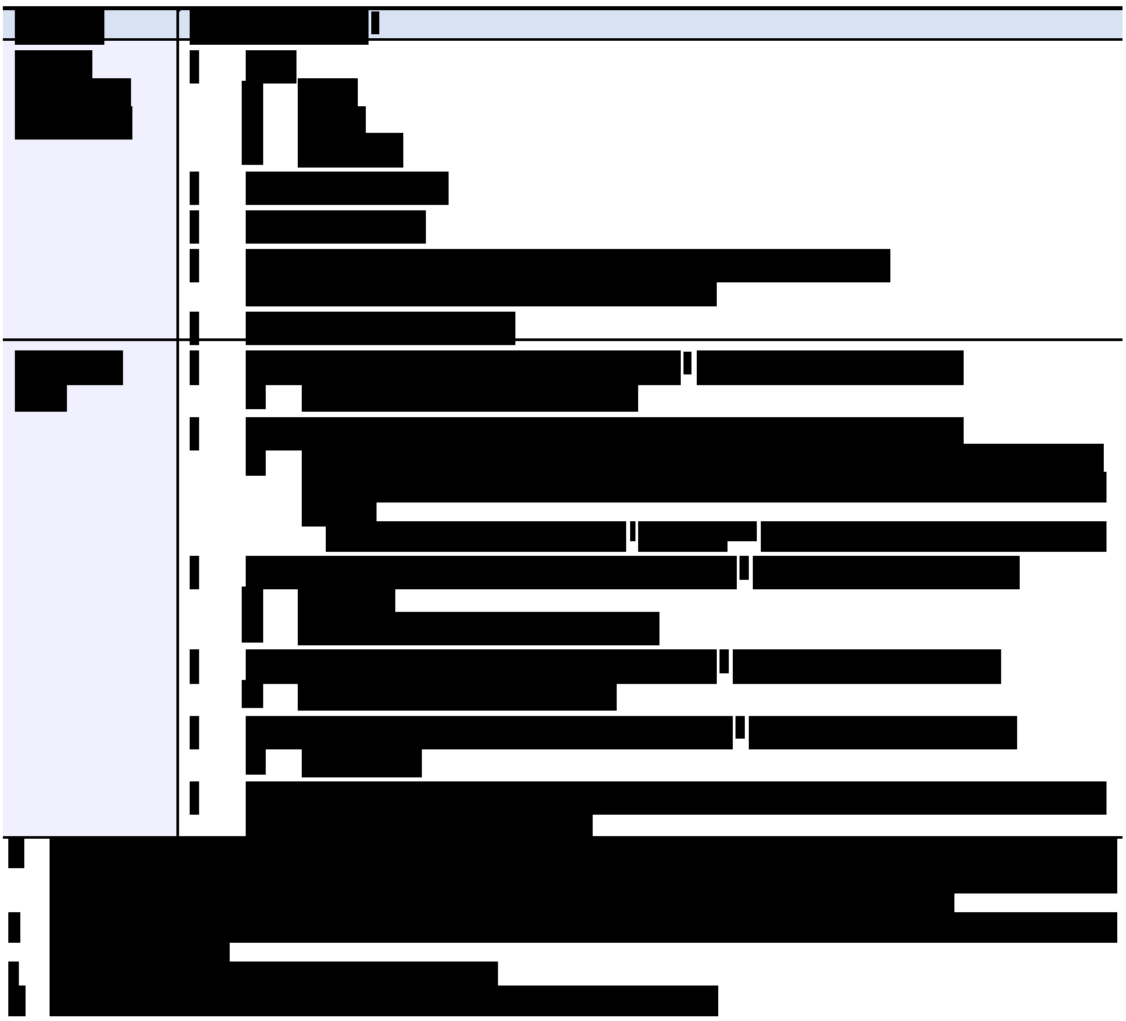


Figure 9.1 Trial Flow Diagram

9.6 Screening / Baseline Tests, Observations, and Windows

Information will be collected and the tests and observations will be performed as shown in Table 9.1 during the period from the consent to the review by CSC. [redacted]





[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

9.7 Pre-procedure Period

9.7.1 Tests and Observations Before the Study Procedure

Twelve-lead ECG should be obtained within 24 hours before performing the procedure.

If the QOL questionnaires (SF-36, KCCQ, EQ-5D-5L) or edema questionnaire are not completely filled in at screening / baseline visit or observation, these questionnaires should be completed before the procedure.

[redacted]



[redacted]

[redacted]

9.8 Preparation of Study Procedure and Device

[redacted]

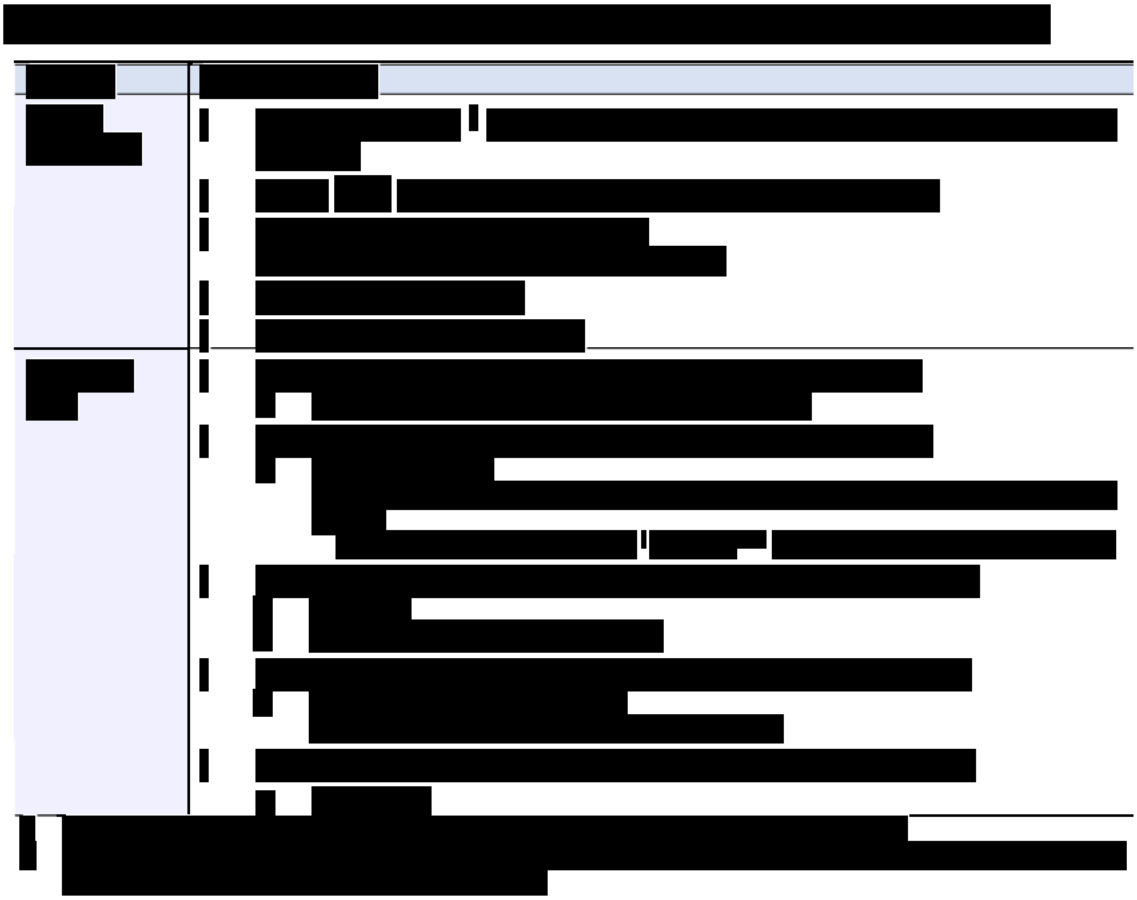
9.9 Tests and Observations During the Procedure

[redacted]



9.10 Tests and Observations Immediately After the Procedure / Before Discharge

[redacted]



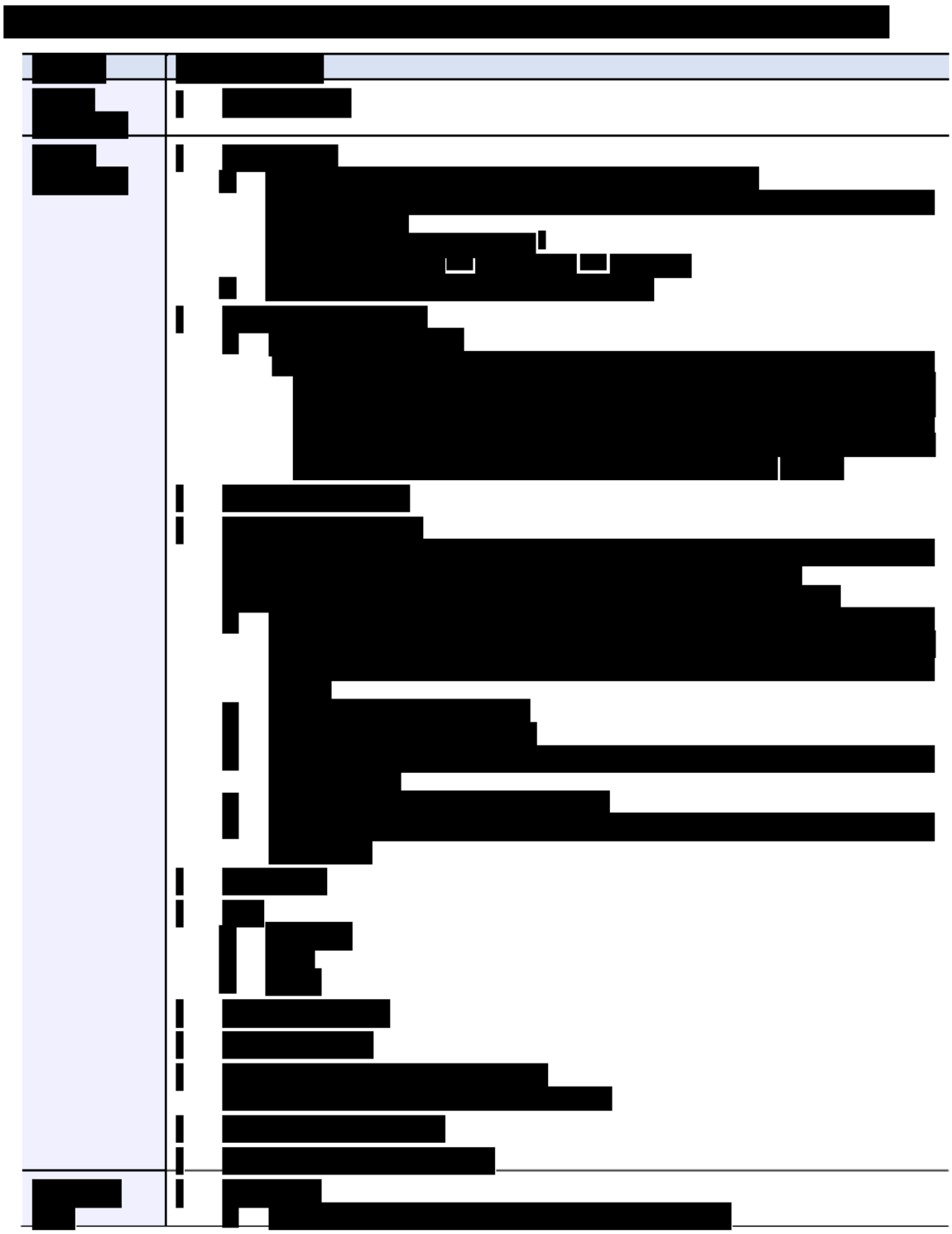
9.11 Tests and Observations at Discharge/7 Days

The tests and observations shown in Table 9.6 will be conducted at [redacted]



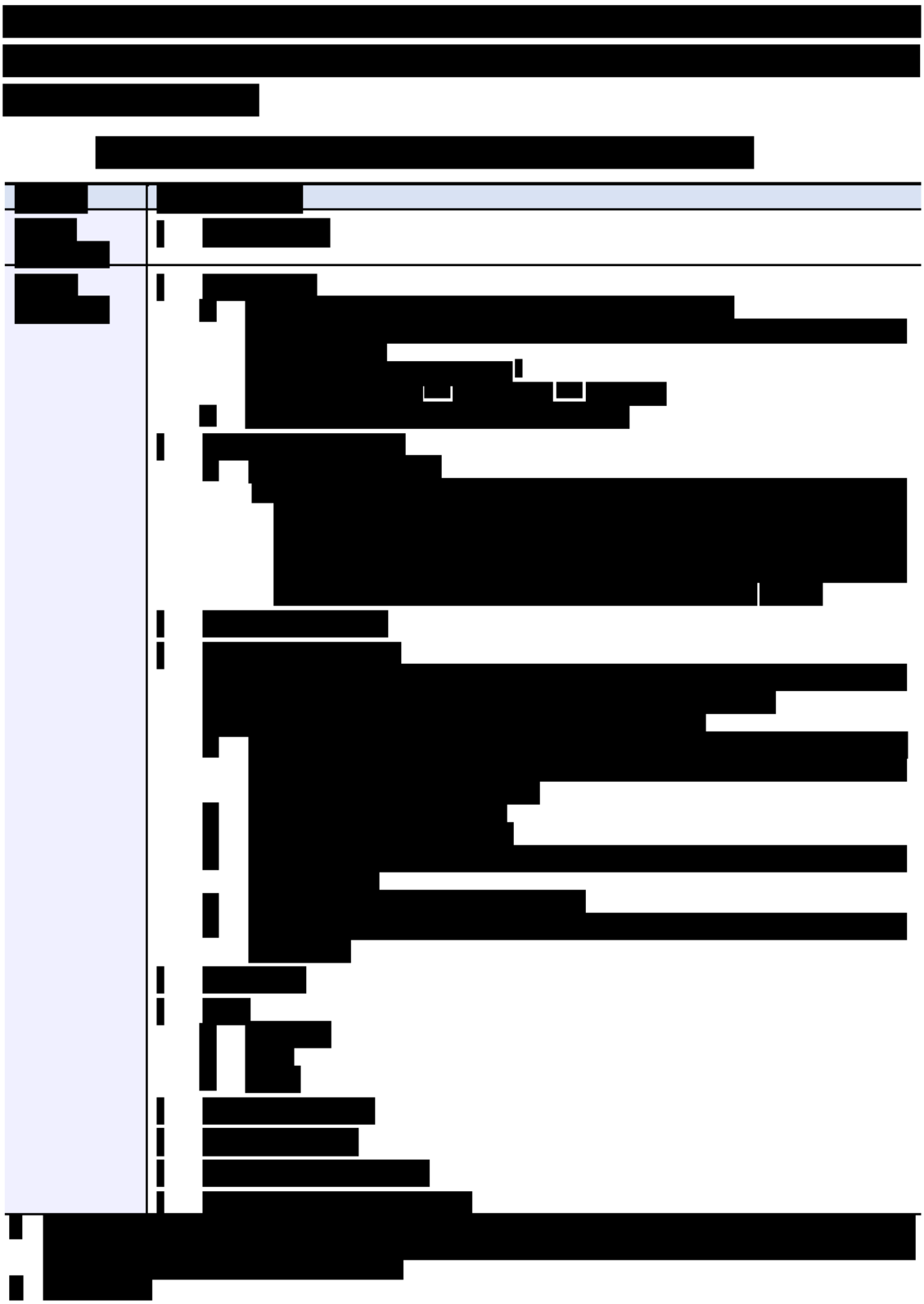
9.12 Tests/Observations and Windows at 30 Days, 6 Months, and 1 Year Post-procedure

[redacted]





9.13 Tests/Observations and Windows at 2 to 5 Years Post-procedure



9.14 Tests and Observations at Unscheduled Visits

[redacted]



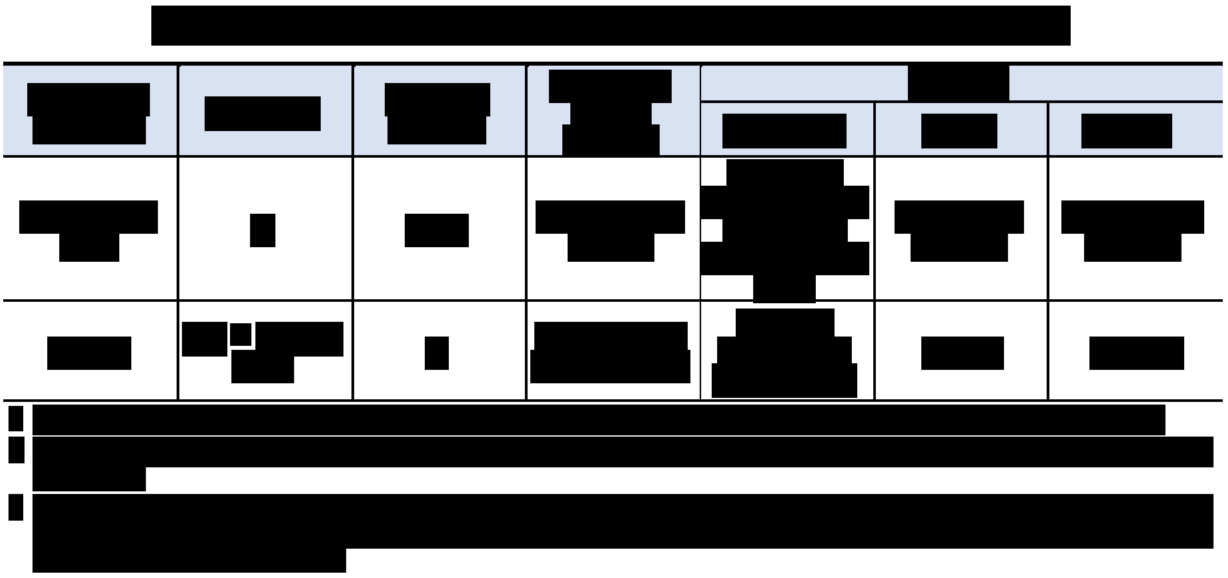
9.15 Tests and Observations at Trial Discontinuation/Exit

[redacted]

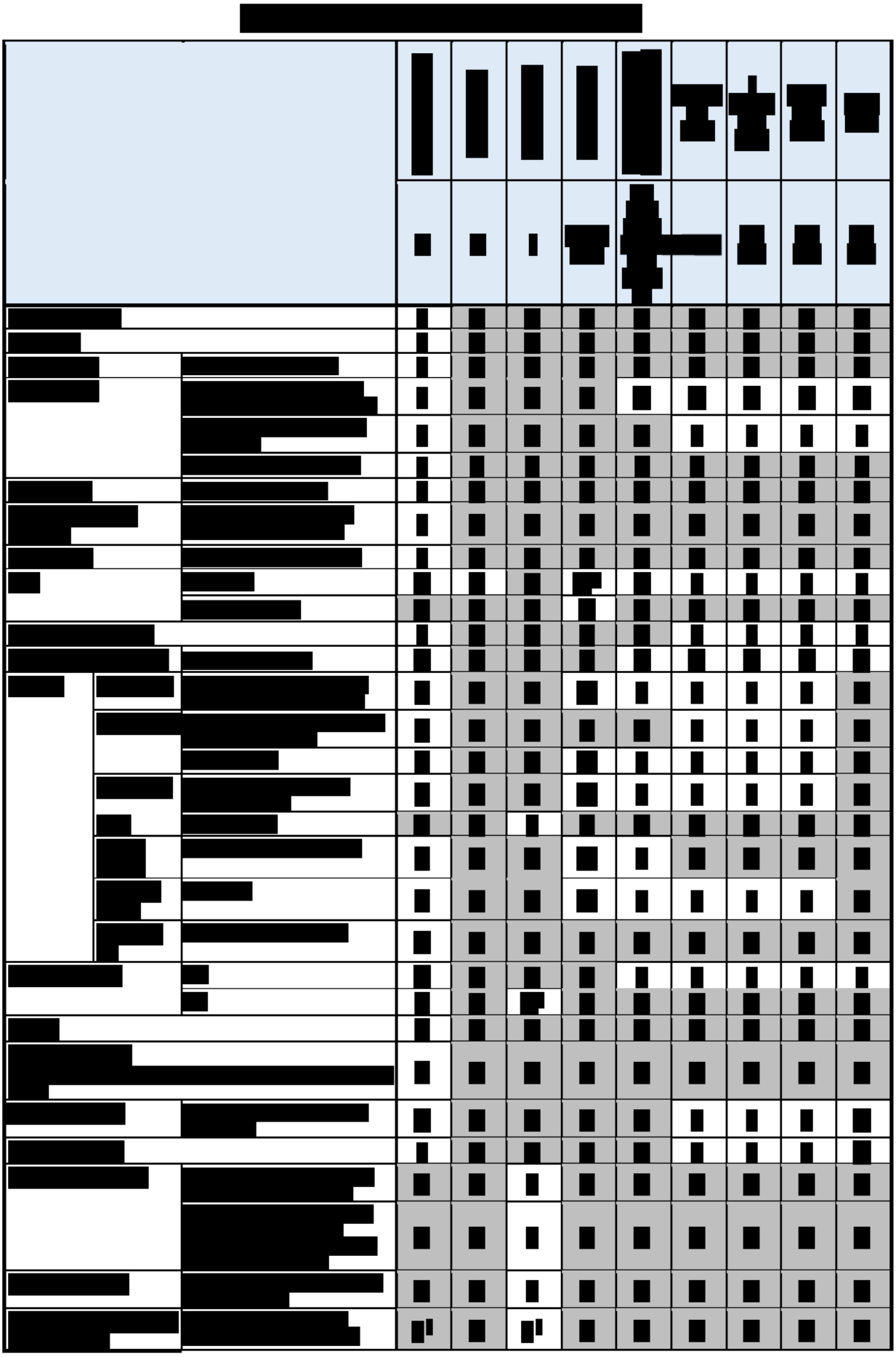


9.16 Timing of Data Collection and Evaluation

[redacted]









9.17 Follow-up for Subjects Who Do Not Make Site Visit

If a subject cannot be followed up because of his/her failure to visit the site, the investigator, etc. will contact the subject as possible to investigate the subject's condition (survival and health status, occurrence of adverse events). In such a case, information including the method of contact, date of contact, condition of the subject, and reason for the failure to visit the site will be recorded in the eCRF. If the subject's whereabouts is unknown despite efforts to contact the subject, it should be documented in the eCRF accordingly along with the date and method of contact.

The follow-up visit will be handled as missing if the subject fails to visit the site after 3 attempts to contact the subject.

10 Concomitant Therapies

10.1 Recommended Anticoagulant/Antiplatelet Therapies

[redacted]

10.1.2 Known thrombosis and bleeding risk factors

The investigator or sub-investigator(s) should take into consideration the thrombosis and bleeding risk factors described in Table 10.1 below as a clinical circumstance for each subject when providing anticoagulant/antiplatelet therapy.

Table 10.1 Known thrombosis and bleeding risk factors

Thrombosis	Bleeding
- previously identified aspirin/clopidogrel resistance - prior history of TIA, stroke or venous thrombosis - spontaneous echo contrast ("smoke") noted preoperatively in the left atrium or left atrial appendage or post-implant in the left atrium or left ventricle - low ejection fraction or stroke volume - arrhythmia (e.g. AF) - dilated left atrium - infection or inflammation - INR post-valve implantation below the target of 2.5	- history of uncontrolled hypertension (> 160 mmHg systolic) - renal disease (dialysis, transplant, Cr > 2.6 mg/dL or > 200 µmol/L) - liver disease (cirrhosis or bilirubin > 2x normal or AST/ALT/AP > 3x normal) - stroke history - prior major bleeding or predisposition to bleeding - labile INR (unstable/high INR, time in therapeutic range < 60%) - age > 65 - medication usage predisposing to bleeding (antiplatelet agents, NSAIDS) - alcohol or drug use history (> 8 drinks/week)

[redacted]

[redacted]

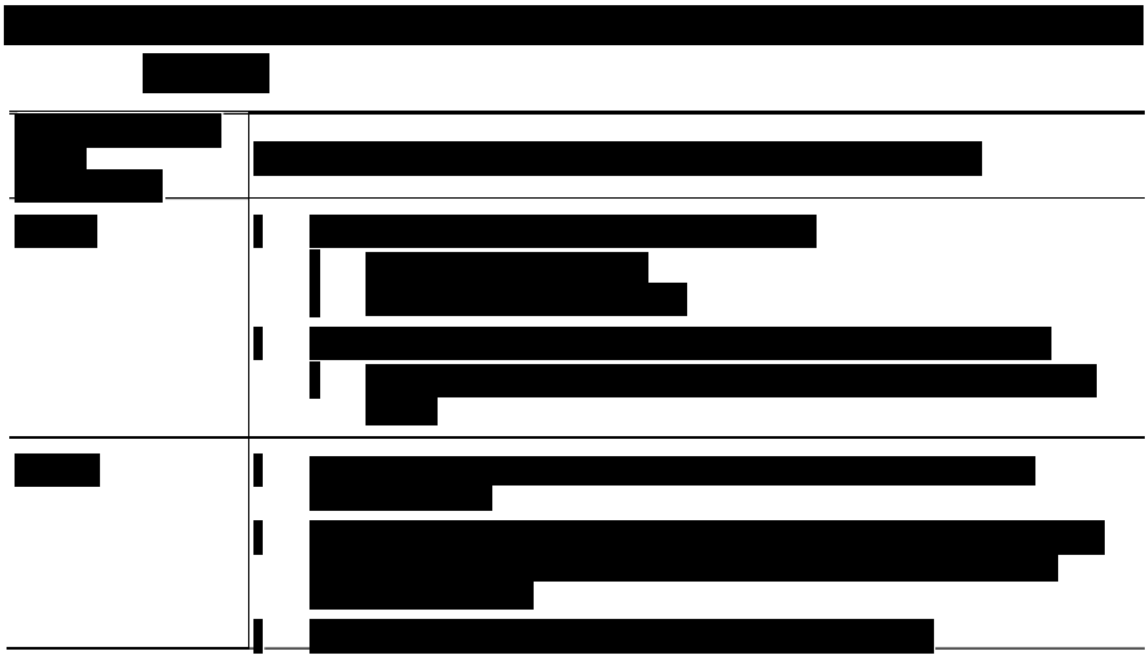




Figure 10.1 Overview of Anticoagulant/Antiplatelet Therapies Recommended in the Trial

[redacted]

10.3 Concomitant Therapies

Pacemaker with leads implanted through the tricuspid valve carries the risk of the leaflet damage or regurgitation caused by the lead. Therefore, treatment should be implemented after careful consideration of the patient's condition, including the use of a leadless pacemaker etc.

10.4 Considerations for Concomitant Therapies and Procedure for Entering Data into Electronic Case Report Form

Subjects who have undergone implantation of this investigational device will receive medical treatment after the procedure at the discretion of the investigator, etc. The medical treatment includes diuretic medications in stable doses, unless patient has documented history of intolerance. [redacted]

If any concomitant therapy is used during the follow-up after the procedure day, the name of the therapy, duration of use, and reason for use should be recorded in the eCRF. If any concomitant medications are used for adverse events and complications which become a risk factor, the name (non-proprietary name) of the drug, duration of treatment, reason for use, route of administration, and dose should be entered in the eCRF.

[redacted]

[redacted]

Use of the drugs for anticoagulant/antiplatelet therapy will be collected [redacted] and entered into the eCRF. Data for anticoagulant/antiplatelet therapy will be collected [redacted].

[redacted]

[redacted]

11 Adverse Events

11.1 Definition of Adverse Event

An adverse event is any untoward or unintended disease or disorder and their signs (including abnormal laboratory findings) in a subject, user, or others during use of the devices for use in the clinical study and which does not necessarily have to have a causal relationship with the device. However, for other persons than the subject, this definition is restricted to events suspected to be related to the devices used in the clinical study.

11.2 Definition of Device Deficiency

A device deficiency is defined as an unfavorable condition broadly related to the quality, safety, performance, etc. of a device used in the clinical study, including breakage and malfunction, whether it occurs in any of the stages of design, delivery, storage, or use.

11.3 Definition of a serious adverse event

A serious adverse event is an event meeting any of the following conditions that occurs in a subject of the clinical study, regardless of the causal relationship with the devices used in the clinical study, according to Article 274, Paragraph 2 of Enforcement Regulations of the Pharmaceutical and Medical Device Act:

a. A case of death
b. A case that may lead to death
c. A case that requires hospitalization in a hospital or clinic or extension of a hospitalization period for treatment
d. A case of disability
e. A case that may lead to disability
f. A case of a serious disease according to cases listed in a. through e. of the preceding item
g. A congenital disease or abnormality in later generations

However, occurrence of a new adverse event or hospitalization which is not accompanied by exacerbation of pre-operative complications (co-mobidity), like the examples shown below, will not be regarded as a serious adverse event and will not require reporting to the sponsor.

- Hospitalization for the treatment planned in the pre-procedure period (e.g. hospitalization for a surgery for the co-mobidities that has become possible after improvement of the heart condition [e.g. cancer surgery], elective PCI)
- Hospitalization for management (e.g. periodical health check-up, hospitalization for tests, educational hospitalization)
- Admission to a rehabilitation institution

In the patient is hospitalized for the purpose of new administration, dose increase, or resumption of tolvaptan, investigator(s) shall examine the handling of this case as a serious adverse event, taking into consideration the treatment background such as worsening of heart failure. If it is determined that the event should not be treated as a serious adverse event based on the clinical circumstances of the subject, the basis of the medical judgment shall be documented in the medical file.

If a serious adverse event occurs, the investigator, etc. will provide appropriate intervention and immediately report to the sponsor accordingly (see Section 11.5 “Handling of a Serious Adverse Event”).

11.4 Assessment of Laboratory Values as Adverse Events

Any remarkable change in laboratory values, ECG, or echocardiogram from baseline that is assessed as an adverse event by the investigator or sub-investigator(s) will be handled as an adverse event.
Any abnormal change in laboratory value that is considered an adverse event will be entered in the adverse event section of the eCRF along with the presence or absence of causal relationship and the reason for the assessment.

11.5 Reporting of Serious Adverse Events

(1) If a serious adverse event occurs after start of the study procedure, or if there is a risk of serious adverse event resulting from any of the deficiencies of the devices used in the clinical study, the investigator or sub-investigator(s) will provide the subject, etc. with appropriate intervention and report accordingly to the sponsor immediately (within 3 calendar days) via oral communication, telephone, e-mail, EDC system or facsimile, regardless of the causal relationship with the devices used in the clinical study.

(2) Subsequently, the investigator (or sub-investigator(s) under the direction of the investigator, if there is a compelling reason) will report the details to the head of the investigational site and the sponsor promptly using “Serious Adverse Event and Device Deficiency Report” or other appropriate forms.

(3) The investigator or sub-investigator(s) and the sponsor will discuss and take appropriate measures, and the investigator will report to the Institutional Review Board of the investigational site to ask for instructions.

(4) If an event is first assessed as nonserious and later re-assessed as serious based on additional information, the investigator must report the details to the sponsor in a timely manner and take the same measures as mentioned above.

(5) After receiving the report, the sponsor will notify all the investigational sites of the information and the measures to be taken, as necessary. The sponsor will also report to the Minister of Health, Labour and Welfare if the case is applicable of Article 274, Paragraph 2

of Enforcement Regulations of the Japanese Pharmaceutical Affairs Law about any serious adverse event suspected to have resulted from the use of the devices used in the clinical study and device deficiency that may cause a serious adverse event.

(6) If the sponsor becomes aware of any serious adverse event or any device deficiency possibly resulting in a serious adverse event which is not anticipated from Clinical Investigator's Brochure, the sponsor will immediately report the deficiency or event to all the investigators and heads of the investigational sites.

(7) The sponsor will submit the listing of subjects with a serious adverse event suspected to have resulted from the use of devices used in the clinical study or a device deficiency which may result in a serious adverse event to all the investigators and heads of the investigational sites every 1 year from the date of first clinical trial notification, etc. within 3 months after expiration of the period.

11.6 Observation Period for Adverse Events

Adverse events will be observed from the beginning of the study procedure until the last observation. Diseases occurring between the consent and the implantation of the investigational device which have not resolved at the time of device implantation will be handled as co-morbidities.

11.7 Recording Adverse Events

(1) Any adverse event occurring in the observation period of this study (except for those shown in Section 11.9 “Events Not Reportable to the Sponsor”) will be entered in the eCRF by the investigator, etc. The investigator, etc. will enter the diagnoses of the adverse events. However, in the case of an extremely severe symptom in the diagnostic category, the event will be documented separately from the original diagnosis. If a definite diagnosis cannot be determined, individual signs or symptoms will be recorded in the eCRF within approximately 14 calendar days.

(2) The investigator or sub-investigator(s) must confirm the outcome of the adverse event occurring in a subject regardless of the causal relationship.

(3) If an adverse event or device deficiency occurs, the investigator, etc. will enter the following information in the eCRF:

(a) Event name:

Document the diagnosis as possible. If the diagnosis is indeterminate, name of the sign or symptom will be entered.

(b) Date of occurrence:

Date of occurrence or exacerbation of a subjective symptom. Date of the examination or test for an abnormal laboratory finding

(c) Seriousness

Assess as either of the following:

1. Serious
2. Nonserious

For the definition of a serious adverse event, see Section 11.3 "Serious Adverse Events."

(d) Intervention with the test device:

Choose one of the following 3 items:

1. No intervention made with the investigational device
2. Explant of the investigational device
3. Others

(e) Other interventions:

Assess as either of the following:

1. No
2. Yes (method of intervention)

(f) Outcome:

Choose one of the following 6 outcomes:

1. Recovered/resolved
2. Recovering/resolving

3. Not recovered/not resolved
4. Recovered/resolved with sequalae
5. Death
6. Unknown

(g) Cause of death (only for an adverse event with fatal outcome)

Choose either of the following 2 items using the definition of "Death" in Section 28 "Definition of Terms" as a reference.

1. Cardiovascular death
2. Non-cardiovascular death

(h) Date of outcome (date of observation)

Enter the date the outcome is assessed. Enter the date of death for fatal outcome and the date of examination or test for an abnormal laboratory finding as the date of outcome. For an adverse event that is assessed as not resolved, follow-up will be performed and additional reports submitted until recovery or stability of the condition, as a general rule, regardless of the causal relationship with the devices used in the clinical study or study procedure, except for the cases of permanent or irreversible adverse event or worsening of a pre-existing complication. In the cases where follow-up until recovery is not considered necessary for permanent or irreversible adverse event or worsening of a pre-existing complication, describe accordingly in the comment section of the eCRF.

(i) Causal relationship with the devices used in the clinical study or study procedure:

The causal relationship with the devices used in the clinical study or the study procedure will be assessed according to the 5 items shown in Table 11.1. For further definition of causal relationship, see Section 28 "Definition of Terms."

Table 11.1 Causal Relationship with Devices Used in the Clinical Trial or Study Procedure (Overview)

	Category	Definition
1	Related	The event is associated with the investigational device or with procedures beyond reasonable doubt.
2	Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably [be] explained by another cause, but additional information may be obtained.
3	Possible	The relationship with the devices used in the study is weak but cannot completely be ruled out. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as “possible”.
4	Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
5	Not related	There is no causal relationship between the event and the devices or procedure.

As necessary, those adverse events assessed as 1 to 3 above will be handled as device related or procedure related adverse events.

An adverse event may be related to both the devices used in the clinical study and the study procedure. Procedure-related complications will be considered “not related” if the device is not used or applied in a patient undergoing the procedure.

In some specific cases, appropriate evaluation of adverse events may be difficult because of insufficient or inconsistent information or inability to verify or supplement the data. The sponsor and the investigator or sub-investigator(s) should avoid such a situation by making their best effort to define and classify the relevant event.

(j) Comments:

In the comment section, enter the following data if there is any relevant information:

- Rationale for assessing the event as an adverse event
- Rationale for assessing the causal relationship with the devices used in the clinical study or study procedure
- Interventions taken for adverse events (e.g. medications or therapies)
- If follow-up of the adverse event is considered not necessary, describe the rationale for that judgement

11.8 Follow-up of Adverse Events

The investigator, etc. will follow up the adverse events that occur until resolution, as a general rule, or stable condition is achieved. Any new information obtained during the follow-up will be reported

by the investigator, etc. to the sponsor.

Note that follow-up is not required if the event meets any of the following conditions while it should be described in the comment section of the eCRF accordingly.

- The event is assessed by the investigator as permanent or irreversible
- The event is assessed by the investigator as equivalent to worsening of the pre-existing complication
- The subject is lost to follow up after occurrence of the event
- Follow-up is considered unnecessary by the investigator, etc. for some other reasons

Also see Section 11.7, “Recording Adverse Events”.

[redacted]

12 Discontinuation or Interruption of the Trial

12.1 Discontinuations in Individual Subjects

12.1.1 Discontinuation Criteria for Individual Subjects

The clinical trial will be discontinued in individual subjects in the cases described below. Trial evaluation will be continued until discontinuation. While the investigational device is implanted, however, the safety of subjects should be ensured and follow-up performed as possible. The investigator or sub-investigator(s) will provide appropriate intervention and treatment to subjects having difficulties in continuing the trial.

The reason for discontinuation should also be documented in the eCRF.

(1) The subject or the legal representative has requested for withdrawal

(2) The investigational device attempted but not implanted

(3) The investigational device once implanted has been explanted as a result of re-intervention

(4) The investigator or sub-investigator(s) has judged that continuation of the trial will be detrimental to the subject's health condition

(5) The subject is not an appropriate study patient as the subject has appeared not to meet the inclusion criteria or to meet any of the exclusion criteria after start of the study procedure

(6) The subject is dead

(7) Subject follow-up is difficult. Subject follow-up will be considered difficult if the subject fails to make a scheduled follow-up visit in 2 consecutive occasions (e.g. follow-up visits at 1 and 2 years)

[redacted]

12.1.2 Procedure for Trial Discontinuation of Individual Subjects

The following procedure should be followed when individual subjects discontinue the trial.

(1) The investigator, etc. will enter the date of discontinuation, reason for discontinuation, and the subject's condition at discontinuation in the eCRF. The subject's safety after discontinuation and related information will also be followed up and documented in the eCRF as possible.

(2) In the case of a discontinuation due to a safety issue resulting from occurrence or worsening of an adverse event, the investigator, etc. will make entries in the eCRF in accordance with Section 11 "Adverse Events." In such a case, the investigator, etc. will perform the follow up of the adverse event.

(3) When a subject is discontinued from the study, the investigator, etc. will inform the sponsor

accordingly in a timely manner.

12.2 Discontinuation or Interruption of Overall Trial

12.2.1 Criteria for Discontinuation or Interruption of Overall Trial

In the following cases, the sponsor will determine whether or not to discontinue or interrupt the overall trial after discussion with the medical advisor.

(1) Continuation of the trial is difficult because of an unanticipated serious adverse event

(2) There is reportedly a risk of significant illness, disorder, or death which may interfere with continuation of the trial

12.2.2 Procedure for Discontinuation or Interruption of Overall Trial

(1) If a decision has been made to discontinue or interrupt the overall trial, the sponsor will immediately notify the head of the investigational sites of the decision in writing.

(2) The head of the investigational site who has received the notification from the sponsor of the decision to discontinue or interrupt the study or to terminate the investigational device development will report it to the investigator and the IRB promptly in writing and provide them with detailed information on the discontinuation or interruption.

(3) When the study has been discontinued or interrupted, the investigator will notify the subjects accordingly in a timely manner and take necessary measures including provision of appropriate medical care.

(4) The investigational sites will return the study materials (including the investigational device) to the sponsor when the study is discontinued or interrupted.

12.3 Discontinuation or Interruption at Individual Investigational sites

12.3.1 Criteria for Trial Discontinuation or Interruption at Individual Investigational sites

The trial will be discontinued or interrupted at the investigational site in the following cases:

(1) The investigator judges that the trial should be discontinued

(2) The head of the investigational site or the IRB judges that the trial should be discontinued

(3) The sponsor judges that the trial should be discontinued at the investigational site because there has been a major protocol deviation and sufficient corrective action has not been taken

(4) The sponsor judges that the trial should be discontinued at the investigational site because of a major violation of the trial contract

12.3.2 Procedure for Discontinuation or Interruption of the Trial at Individual Investigational sites

(1) Discontinuation or interruption at the discretion of the investigator

The head of the investigational site who has received the notification from the investigator of the decision to discontinue or interrupt the trial will report it to the sponsor and the IRB promptly in writing.

(2) Discontinuation or interruption at the discretion of the head of the investigational site or the IRB

The head of the investigational site will notify the sponsor, the investigator, and the IRB of the decision to discontinue or interrupt the trial at their own discretion or by the judgment of the IRB in writing in a timely manner.

(3) Trial discontinuation decided by the sponsor

The head of the investigational site who has received the notification from the sponsor of the decision to discontinue or interrupt the trial will report it to the investigator and the IRB promptly in writing and provide them with detailed information on the discontinuation or interruption.

The investigational sites will return the trial materials (including the investigational device) to the sponsor when the trial is discontinued or interrupted.

The sponsor will promptly notify the heads of all the investigational sites and the regulatory authority in writing of the discontinuation or interruption of the trial and its reason. When the trial has been discontinued or interrupted, the investigator will notify the subjects accordingly in a timely manner and take necessary measures including provision of appropriate medical care to subjects.

13 Trial Completion

The overall trial is considered completed when the protocol-specified planned number of subjects for the main cohort is reached and the observation of the last subject enrolled is completed. At the completion of the last patient's follow-up period (1 year) for primary endpoints, clinical study report will be created and submitted as part of the approval application. Thus, this study may be terminated based on the marketing approval of EWJ-202 before the last enrolled patient completes the follow-up at 5 years post-procedure. If the trial is completed with the marketing approval, the clinical trial will be changed to a post-marketing clinical study promptly after obtaining the marketing approval and will be continued until the last enrolled patient completes the follow-up at 5 years post-procedure. See Section 27 "Handling at the Time of Marketing Approval."

The investigational site should take the following procedures to complete the trial:

(1) When the trial is completed at the investigational site, the investigator will notify the head of the investigational site of the study completion in writing and submit the report of trial results as specified by the site.

(2) The head of the investigational site who has received the notification from the investigator of the trial discontinuation will inform the IRB and the sponsor accordingly in writing in a timely manner, and report an outline of the trial results based on the report submitted by the investigator.

(3) The sponsor will implement the procedure for trial completion at the investigational site. The investigator and the head of the investigational site will implement the procedure for trial completion as specified by the investigational site.

(4) The investigational sites will return all the trial materials (including the investigational device) to the sponsor when completing the trial.

14 Statistical Analysis

14.1 Analysis populations

The following analysis populations for main and roll-in cohort will be defined.

(1) Enrolled Population – Safety

[redacted]

(2) Enrolled Population – Effectiveness

[redacted]

(3) As-Treated Population

[redacted]

(4) Per Protocol Population

[redacted]

[redacted]

[redacted]

14.2 Statistical Analysis Items and Plan

14.2.1 Primary Endpoint

The primary endpoint of the trial was two co-primary endpoints of all-cause mortality and heart failure hospitalization at 1 year after the procedure.

[redacted]

[redacted]

14.2.2 Secondary Endpoints

[Effectiveness]

Descriptive statistics for each of the secondary endpoints will be calculated at each assessment, pre-specified observation period. The change from baseline to each observation period will be presented in the same way. [redacted]

(1) TR grade
(2) NYHA functional class
(3) QOL
(4) 6MWD

[Safety]

For the composite major adverse event (MAE) to be evaluated as a secondary endpoint, descriptive statistics such as the number of patients with event, the number of events, event rate during the defined observation period will be calculated. [redacted]

Details will be specified in a statistical analysis plan to be prepared separately.

(1) Composite of Major Adverse Events (MAEs)
(2) Individual components of MAEs
(3) All-cause mortality
(4) HF Hospitalization
(5) All-cause Hospitalization
(6) Durable RVAD implantation or heart transplant
(7) Tricuspid valve surgery or percutaneous tricuspid intervention
(8) Need for paracentesis

In addition to the secondary safety endpoints, a summary of the percentage of patients who experience an early adverse event [redacted] and late adverse event [redacted] will be reported [redacted].

14.2.3 Exploratory Endpoints

[redacted]

14.2.4 Additional Outcomes

[redacted]

14.2.5 Other Exploratory Analysis

[redacted]

14.2.6 General Conventions

(1) Descriptive statistics for continuous values are mean values, standard deviations, two-sided 95% confidence interval for mean values (as t-distribution unless otherwise specified), median, min, max, and the number of patients.

(2) The number and percentage of patients in each category will also be obtained for descriptive statistics for discrete values. The two-sided 95% confidence interval by the exact method will also be obtained if needed.

(3) Descriptive statistics will be calculated in each observation period, and the changes from baseline to each observation period will also be calculated.

(4) Paired data (when data both at baseline and in each observation period are available for each patient) will be presented as "paired," and unpaired data will be presented as "unpaired."

(5) Paired t test (Wilcoxon signed rank test in non-parametric cases) or one-sample t test will be conducted for the changes from baseline to each observation period, if needed.

(6) Fisher's exact test, if appropriate, will be used for two-group comparison of nominal scales such as sex, and Wilcoxon rank-sum test will be used for ordinal scale data such as NYHA classification.

(7) The time-to-event summaries will include information such as the number of at-risk subjects, the number of subjects with events, etc. For patients who did not have an event but remain in the trial, they will be censored at the last time their status is confirmed. Time to first event curves will be constructed using Kaplan-Meier estimates.

(8) The significance level will be two-sided 5%, unless specified otherwise.

(9) All analysis will be performed using SAS version 9.4 or the latest release version at the time of analysis unless otherwise specified.

14.3 Handling of Missing Data and Abnormal Data etc.

(1) Missing data will be treated as missing, and imputation will not be conducted. Thus, missing data at baseline or at each observation period will be excluded from the analysis unless otherwise specified. Additional details will be provided in the SAP.

(2) The handling of cases in which the date of onset of adverse events or the date of initiation of drug administration during follow-up is unknown is separately specified in the statistical analysis plan.

(3) Handling of the matters which are not stipulated in this protocol will be determined before fixation of the case. Details about handling will be described in the clinical study report.

14.4 Statistical Analysis Plan

14.4.1 Preparation of Statistical Analysis Plan

The person in charge of statistical analysis will prepare a statistical analysis plan including detailed descriptions for the matters described in Section 14.2 "Statistical Analysis Items and Plan"

14.4.2 Revision of Statistical Analysis Plan

When a change is made in the analysis plan, appropriateness of the changes and their effects on evaluation of this clinical trial will be examined, and whether or not the change is acceptable will be decided. When changes are made, a history describing the details of the change, reasons and the like will be documented and the statistical analysis plan will be revised.

14.4.3 Deviation from Statistical Analysis Plan

All deviations from the statistical analysis plan will be described in the study report.

15 Electronic Case Report Form

15.1 Procedure and Precautions for Preparation of Electronic Case Report Form

(1) The investigator, etc. will use the EDC system to prepare eCRF.

(2) The investigator, etc. will prepare eCRF for each subject.

(3) Entries in eCRF will be made by the investigator, sub-investigator(s), and clinical research coordinator(s) based on the data collected in accordance with the protocol. In addition to the investigator, those designated in “List of Sub-investigator(s) and Clinical Research Coordinator(s)” may enter data in the eCRF. However, the clinical research coordinator may enter data only when no medical judgement is involved.

(4) The sponsor will explain how to enter and correct data in the eCRF according to "Electronic Case Report Form (e-CRF) Completion Manual" to the investigator or sub-investigator(s) and the clinical research coordinator.

(5) The investigator, etc. will prepare eCRF for each subject promptly after completion of observation (within 14 calendar days).

(6) The investigator will confirm the accuracy and validity of the data and sign the eCRF before submitting it to the sponsor.

(7) The investigator will retain the original eCRF submitted by the investigator. The investigational site or the investigator will retain a copy of the eCRF that has been submitted.

15.2 Change or Correction of eCRF Entries

(1) Changes and corrections may be made before signing the eCRF. However, when changing or correcting important information (e.g. information related to consent, adverse event term and causal relationship), the reason for the change or correction should be documented in the relevant section.

(2) Any change or correction after signing the eCRF will requires the signature to be placed again in addition to (1) above.

16 Access to Source Documents/Data

16.1 Direct Access to Medical Information (Source Document)

The investigator and the investigational site should cooperate for the monitoring and auditing by the sponsor, the contract research organization, and others and the inspections and investigations by the IRB and regulatory authorities. In these situations, all trial-related records including the source documents should be made available for direct access. Before the direct access takes place, the sponsor will discuss the time, method, documents and data to be accessed, and other issues with the investigator and the investigational site.

Careful attention should be paid to ensure appropriate protection of the subject’s privacy if subject’s

medical information is made available for direct access.

The source documentation may consist of but is not limited to operative or procedure reports, anesthesia records, progress notes, discharge summaries, laboratory, reports, radiographic reports, medication logs, and worksheets. Source Documents may be in electronic form and/or hard (paper) copies.

16.2 Identification of Any Data To Be Recorded Directly on the eCRFs and To Be Considered To Be Source Data

The following data will be recorded directly on the eCRFs and considered to be source data.

- Subject eligibility
- Adverse event information including seriousness, teatment, outcome, cause of death, causal relationship with the devices used in the clinical trial or study procedure, and comments
- Name of device deficiency, details of the deficiency
- Details of follow-up of subjects who fail to make site visits
- Date of discontinuation and reason for discontinuation
- Other medical opinions of the investigator, etc.

17 Compliance with, Deviation from, or Change to the Protocol

17.1 Deviation from or Change to the Protocol

The investigator or sub-investigator(s) should not implement any deviation from or change to the protocol without prior written agreement between the investigator and the sponsor and the prior review and documented approval/favourable opinion from the IRB.

(1) If the monitoring, etc. reveals a deviation from the protocol that has not been approved in advance by the sponsor or the head of the investigational site and the IRB via the head of the investigational site, or has not been agreed upon in advance by the sponsor, the investigator or sub-investigator(s) will document all the deviations or changes. In addition, actions should be taken to prevent occurrence of subsequent deviation or change.

(2) If a protocol amendment seems to be necessary based on the details and reasons for the deviation from or change to the protocol, the investigator submit the amended protocol including the draft to the IRB via the sponsor and the head of the investigational site as soon as possible to obtain its approval.

(3) In the case of a change to the protocol, the investigator should obtain prior written agreement between the sponsor and the investigator, and report the change to the protocol to the IRB via the head of the investigational site.

(4) The investigator and the sponsor will obtain the document concerning the direction and decision by the head of the investigational site.

17.2 Deviation from or Change to the Protocol for Compelling Medical Reasons

(1) If the investigator has implemented a deviation from, or a change of, the protocol for a compelling medical reason to eliminate an immediate hazard to trial subjects, the investigator or sub-investigator(s) should document all the actions that deviated from or changed the protocol. The investigator will prepare the record explaining the reason, submit it to the sponsor and the head of the investigational site, and retain its copy.

(2) The investigator and the sponsor will obtain the document concerning the direction and decision by the head of the investigational site.

18 Record Retention

18.1 Institutional Review Board

The head of the investigational site or the IRB provider will retain the trial-related documents or records to be retained by the IRB as stipulated in the GCP Ordinance for Medical Devices to the date of (1) or (2), whichever comes later:

(1) The day the medical device related to the investigational device is approved for marketing (the day when the notification is received, if the notification has been sent of the decision that the data of the clinical trial results specified in Article 32, Paragraph 3 of the GCP Ordinance for Medical Devices will not be attached to the application for marketing approval specified in Article 14, Paragraph 3 of the Pharmaceutical Affairs Law)

(2) Three years after termination or completion of the clinical trial

18.2 Investigational sites

The person responsible for retention of records designated by the head of the investigational site will retain the trial-related documents or records to be retained at the investigational site as stipulated in the GCP Ordinance for Medical Devices to the date of (1) or (2), whichever comes later:

(1) The day the medical device related to the investigational device is approved for marketing (3 years after the day when the notification is received, if the notification has been sent of the decision that the data of the clinical study results will not be attached to the application for marketing approval according to Article 32, Paragraph 3)

(2) Three years after termination or completion of the clinical trial

However, in the cases where the retention for the above-mentioned period appears to be difficult for some reason of the investigational site or the sponsor needs retention for a longer period, the sponsor will discuss the duration and method of retention with the investigational site.

18.3 Sponsor

The sponsor will retain the trial-related documents or records to be retained by the sponsor as stipulated in the GCP Ordinance for Medical Devices to the date of (1) or (2), whichever comes later:

(1) Five years after the marketing approval of the medical device related to the investigational device (or 3 years after the decision to terminate the development)

(2) Three years after termination or completion of the clinical trial

The sponsor will notify the IRB provider and the head of the investigational site accordingly when retention is no longer necessary for the trial-related records to be retained by the IRB provider and the head of the investigational site.

19 Quality Control and Quality Assurance

19.1 Quality Control

Monitoring will be performed to confirm the progress of the clinical trial and whether the trial is being conducted in accordance with the GCP Ordinance for Medical Devices, Enforcement Regulations, and the current protocol in order to ensure proper conduct of the trial from the perspectives of assurance of reliability of the trial and protection of subjects.

(1) The investigator, sub-investigator(s), clinical research coordinator(s), and study device controller will confirm that the clinical trial is being conducted in compliance with the protocol and GCP Ordinance for Medical Devices in order to control the quality of the clinical trial at the investigational site. For that purpose, the investigational site will accept the direct access by the sponsor and the contract research organization to the source data, medical record, and other trial-related records.

(2) The monitors of the sponsor and the contract research organization will perform monitoring to confirm that the clinical trial is being conducted appropriately at the investigational site in compliance with the protocol and GCP Ordinance for Medical Devices, and carry out the direct access to source documents and other data to ensure that eCRF entries are correct.

(3) The monitors of the sponsor and the contract research organization, the person in charge of quality control, the data controller, and the statistician will check and confirm the quality of data at each stage of data handling.

19.2 Quality Assurance

Audits will be performed to confirm whether the trial has been conducted in accordance with the GCP Ordinance for Medical Devices and the protocol in order to ensure the reliability of the data collected in this trial from the perspectives of assurance of trial reliability and protection of subjects. The audits will be performed by individuals who are independent of the trial monitoring or quality control function, and will be evaluated separately.

(1) In order to ensure the conduct of the clinical trial in compliance with the protocol and GCP Ordinance for Medical Devices and the quality of eCRF entries, the investigational site will accept the direct access to and investigation of the source data, medical records, and other trial-related records by the auditors of the sponsor and the contract research organization.

(2) The auditors of the sponsor and the contract research organization who are independent of the monitoring function will perform audits at the sponsor, the contract research organization, and as necessary the investigational sites to assure the quality of the clinical trial by confirming that the clinical trial is being conducted appropriately in compliance with the protocol and GCP Ordinance for Medical Devices.

20 Control of Devices Used in the Clinical Trial

20.1 Delivery of Devices To Be Used in the Clinical Trial

After entering into the trial contract with the investigational site, the sponsor will deliver the devices used in the clinical trial to the investigational site. The sponsor will also provide the written procedure for controlling the devices used in the clinical trial which specifies the handling, control and storage, and recording of the devices used in the clinical trial at the time of delivery or promptly after delivery.

20.2 Storage and Control of the Devices for Use in the Clinical Trial

The study devices will be stored and controlled by the head of the investigational site or by the study device controller designated by the head of the investigational site in accordance with the written procedure for controlling the devices used in the clinical trial provided by the sponsor.

The investigational site will verify the receipt of the devices used in the clinical trial that have been delivered, the devices in stock, use of the devices by each subject, the devices used in the clinical trial that have not been used, and return of the devices used in the clinical trial described later in Section 20.3 according to the written procedure for controlling the devices used in the clinical trial, and prepare the records.

The records will be kept in the device accountability record, including the date, quantity, manufacturing number or code, expiry, and subject identification code.

20.3 Return of Devices for Use in the Clinical Trial

The devices for use in the clinical trial that remain unused will be returned to the sponsor in cases where, for example, the device appears to be expired or the subject enrollment is completed. The devices for use in the clinical trial that remain unused will be returned whether the package has been opened or not. The devices for use in the clinical trial which appear to have a deficiency during the trial will also be returned to the sponsor as possible.

21 Evaluation of the Trial by Clinical Study Boards

21.1 Echo Core Lab

In this trial, echo core lab will be established as an organization independent of the sponsor and individual investigational sites in order to evaluate the echocardiogram data taken at the investigational sites objectively and uniformly. [redacted].

The echo core lab will perform measurement of the endpoints specified in this protocol and eCRF based on the image data submitted by the investigational site.

21.2 Central Screening Committee

In this trial, CSC will be established as an organization in order to evaluate objectively and uniformly the patient eligibility that has been assessed by Local Heart Team. [redacted]. CSC will review the case information submitted, and assess the eligibility as to whether the patient can be an appropriate subject of the trial.

The investigational sites will cooperate to provide as much patient information as possible in response to the request from CSC.

21.3 Clinical Event Committee

In this trial, Clinical Event Committee will be established as an organization independent of the sponsor and individual investigational sites in order to evaluate prespecified adverse events occurring in the trial period objectively and uniformly. CEC, consisting of members with expertise on the target disease and treatment, will assess the adverse events for causal relationship with the devices used in the clinical trial .

For the procedure of Clinical Event Committee, refer to “CEC Charter.”

The investigational sites will cooperate to provide as much subject information as possible in response to the request from Clinical Event Committee.

The source documents required for assessment of the events include, but not limited to, the following:

- Death certificate
- Medical record
- Image diagnosis records including echocardiogram, CT and MRI scans
- Discharge note
- Autopsy record (if available)

21.4 Data Monitoring Committee

In this clinical trial, Data Monitoring Committee* (DMC) will be established as an organization independent of the sponsor and the investigator, etc. in order to secure the subjects' safety and to ensure the ethical and scientific validity of the trial conduct. DMC will evaluate the data obtained during the trial in an unbiased manner, and based on these results, provide proper advice and recommendations to the sponsor.

Refer to separate "Data Monitoring Committee Charter" for requirements for holding a DMC meeting, contents of the meeting, and operating procedure,etc.

[redacted]

22 Ethical Considerations and Legal Provisions

22.1 Compliance with GCP Ordinance for Medical Devices

This clinical trial will be conducted in compliance with "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (Law No. 145, 1960), ethical principles that have their origin in the Declaration of Helsinki and "Ministerial Ordinance on Standards for Clinical Studies of Medical Devices" (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 36, dated March 23, 2005), "Ministerial Ordinance that Partially Amends the Ministerial Ordinance Concerning the Standards for Clinical Studies of Medical Devices" (MHLW Ordinance No. 68, dated March 31, 2009) and related notifications, and this protocol.

22.2 Delegation of Trial-related Duties at Investigational Site

(1) If part of the trial-related duties are to be delegated to the sub-investigator(s) or clinical research coordinator(s), the investigator should prepare a list showing what duties will be delegated to whom, and submit the list to the head of the investigational site in advance.

(2) The head of the investigational site will designate the sub-investigator(s) and clinical research coordinator(s) based on the list prepared by the investigator, submit the list to the investigator and the sponsor, and retain a copy of the list.

(3) The investigator will fully explain about the protocol, handling of the devices for use in the clinical trial, and other trial-related duties to the sub-investigator(s) and clinical research coordinator(s), and provide information necessary for proper and smooth conduct of the trial-related duties. Information on trial-related duties that becomes available after initiation of the trial such as changes to the protocol will also be provided to the sub-investigator(s) and clinical research coordinator(s) in a timely manner.

22.3 Preparation of Subject Consent Document Form and Written Information

(1) The investigator will prepare the consent document form and written information with the assistance of the sponsor. Ethical principles that derive from GCP Ordinance for Medical Devices should be complied with in preparing and amending the written information. The language used in the written information should be easy for subjects to understand.

(2) The following information should be included in the consent document form and written information for subjects:

- (a) That the trial involves research
- (b) The purpose of the trial
- (c) Name and contact information of the investigator
- (d) Method of the trial (including the investigational aspect of the trial and inclusion/exclusion criteria of subjects).
- (e) Expected clinical benefit and risk or inconvenience

(f) Availability of other treatment options for the subject, and their anticipated significant benefits and risks

(g) Planned duration of the subject's participation in the trial

(h) That the subject's participation in the trial is voluntary, and the subject or his/her legal representative may refuse to participate in or withdraw from the trial at any time that the subject will neither be unfavorably treated because of the refusal or withdrawal nor lose any benefit to which the subject is otherwise entitled

(i) Information on handling of the investigational device for a subject who discontinues participation in the trial

(j) That the monitors, the auditors, the IRB, and the regulatory authorities will have access to the source data That in such a case, the confidentiality of subjects will be maintained that, by signing the consent document, the subject or his/her legal representative is authorizing such access

(k) That the subject's confidentiality will be maintained if the results of the trial are published

(l) Contact information at the medical institution for inquiries or communication in case that subjects need more information for the trial and the right of the subjects, or that subjects suffer any trial-related health injury

(m) Compensation and medical treatment available for subjects for trial-related health injuries

(n) Planned number of subjects participating in the trial

(o) That the subject will be informed of any information that may affect their willingness to continue the trial as soon as such information is made available

(p) The circumstances or reasons under which the subject's participation in the trial may be terminated

(q) Breakdown of expenses, if any, to be paid by the subjects

(r) Breakdown of financial rewards, if any, to be given to the subject (e.g. agreement on the calculation of the payment)

(s) Requirements that subjects should follow

(3) The following procedures should be taken to amend the informed consent document for subjects:

The investigator will amend the IRB-approved informed consent document as necessary based on new information, for example, when new significant information becomes available that can be relevant to the subjects consent. After the amended informed consent document is approved by the IRB, the investigator will provide the subject with the new significant information and related matters and obtain the written consent again.

22.4 Matters Related to Subjects' Privacy

(1) The investigator, etc. will enter the subject identification code, not the medical record number, in the eCRF. If any subject identifier, such as the subject's name, is displayed on any other documents or materials (e.g. examination slip), the identifier should be deleted before the documents/materials are submitted to the sponsor.

(2) The investigator or sub-investigator(s) will inform the subject that the confidentiality of personal information will be maintained when the monitors and auditors of the sponsor or IRB or regulatory authorities directly access the trial-related records including source documents, when the information is used for application for marketing approval of the medical device, and when the trial results are published.

23 Matters Related to Administration Including Expenses

23.1 Clinical Trial Costs

The trial costs will be funded by the sponsor, Edwards Lifesciences Japan LLC.

23.2 Compensation/Insurance for Subjects

The sponsor will prepare the compensation system in case of health hazard in subjects. When a health injury occurs from participation in this trial, medical fees, medical benefits, and compensation will be paid according to the sponsor's compensation system. However, the same shall not apply in the following cases:

(1) Health injuries with obvious liability, such as those due to intention or gross negligence of the investigational site (including violation of GCP Ordinance for Medical Devices, significant deviation from the protocol)

(2) Health injuries due to intention of the subject

23.3 Payment of Money to Reduce Subject's Burden

The expense to reduce the trial-related burden on subjects will be paid by the sponsor to the investigational sites at the prespecified time point according to the contract with the investigational sites.

24 Agreement on Protocol

The investigator and the sponsor will agree on the contents of the protocol and sign the attached sheet as an evidence of agreement to comply with this protocol.

25 Protocol Changes

The changes in protocol can be made only by written amendments agreed upon by the Sponsor. The amended protocol will be submitted to the required regulatory agencies before being distributed to sites, as appropriate. Each site must obtain IRB approval and complete required training.

26 Policy for Use or Publication of Trial Results

(1) Any information on the investigational device as well as the unpublished information provided by the sponsor, including information on clinical use of the investigational device, its structure, performance, principle, and other scientific data related to the investigational device will be handled as confidential information. The investigator or sub-investigator(s) will use such information solely for the conduct of this clinical trial and must not use it for any other purposes without prior written approval of the sponsor.

(2) By signing the agreement on the protocol, the investigator will agree on the use of the trial results by the sponsor for application for marketing approval of the medical device in

Japan, for publication, and as information for experts in the fields including medicine.

(3) The trial will be registered in a publicly accessible database.

27 Handling at the Time of Marketing Approval

27.1 Change to a Post-marketing Clinical Study

After the marketing approval is granted, this clinical trial will be changed to a post-marketing clinical study. The term “clinical trial” in this protocol and CRF will be replaced by “post-marketing clinical study” as appropriate. “Ministerial Ordinance on Standards for Clinical Studies of Medical Devices” (MHLW Ordinance No. 68, dated March 31, 2009) will be replaced by “Ministerial Ordinance on Standards for Clinical Studies of Medical Devices” (MHLW Ordinance No. 68, dated March 31, 2009) and “Ministerial Ordinance on Standards for Post-marketing Surveillance and Clinical Studies of Medical Devices” (MHLW Ordinance No. 38, dated March 23, 2005) (however, this shall not apply to this section).

27.2 Marketing Approval

The procedure for completing the trial will be implemented according to Section 13 “Trial Completion” when the investigational device is approved for marketing and this clinical trial is to be completed (the replacement described in Section 27.1 “Change to a Post-marketing Clinical Study” will not apply at this time).

28 Definition of Terms

Terms including adverse event are defined below:

Term	Definition
Access site (VARC-1)	Any location (arterial or venous) traversed by a guidewire, catheter or sheath used during the procedure for delivery of the device.
Access site and Vascular Complications (MVARC [60])	**I. Vascular complications** A. Major access site vascular complications, including: i. Aortic dissection or aortic rupture, or ii. Access site-related† arterial or venous injury (dissection, stenosis, ischemia, arterial, or venous thrombosis including pulmonary emboli, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect‡), irreversible nerve injury, or compartment syndrome resulting in death; life-threatening, extensive, or major bleeding (MVARC primary bleeding scale); visceral ischemia; or neurological impairment iii. Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage, or iv. Unplanned endovascular or surgical interventions resulting in death; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischemia; or neurological impairment B. Minor access site vascular complications, including: i. Access site arterial or venous injury (dissection, stenosis, arterial, or venous thrombosis including pulmonary emboli, ischemia, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect‡) not resulting in death; hemodynamic compromise; life-threatening, extensive, or major bleeding (MVARC primary bleeding scale); visceral ischemia; or neurological impairment, or ii. Distal embolization treated with embolectomy and/or thrombectomy not resulting in amputation or irreversible end-organ damage, or iii. Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication, or iv. Vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) **II. Cardiac structural complications due to access-related issues** A. Major cardiac structural complications, including: i. 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: i. Cardiac perforation* or pseudoaneurysm not meeting major criteria * Including the left ventricle, left atrium, coronary sinus, right atrium, and right ventricle. † May arise from the access procedure per se or complications from vascular closure devices. ‡ Meeting pre-specified criteria for a hemodynamically significant shunt, or requiring unplanned percutaneous or surgical closure.
Adverse Device Effect (ADE) (ISO 14155:2011)	Adverse events related to the use of study device Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device
Adverse Event (AE) (ISO 14155:2011)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device

Term	Definition
	Note 1: This definition includes events related to the investigational medical device or the comparator Note 2: This definition includes events related to the procedures involved Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices
Arrhythmia and conduction disorder requiring permanent pacing	**Arrhythmia** A condition in which the heart beats with an irregular or abnormal rhythm. An arrhythmia may cause symptoms and/or hemodynamic instability, and may require medical/pharmaceutical intervention, electrical conversion, and/or placement of a permanent pacemaker. **Conduction system disorders** An impairment of the electrical pathways and specialized muscular fibers that conduct impulses through the heart (ex. Bundle branch block, heart block, etc.). A conduction system disorder may require placement of a temporary or permanent pacemaker.
Bleeding (MVARC[60])	**I. Minor** Any overt†, actionable sign of hemorrhage that meets ≥ 1 of the following, and otherwise does not meet criteria for major, extensive, or life-threatening bleeding: (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) • Requiring nonsurgical medical intervention by a health care professional • Leading to hospitalization or increased level of care • Prompting evaluation • Requires 1 or 2 units of whole blood or packed red blood cell (RBC) transfusion **II. Major** Overt bleeding either associated with a drop in the hemoglobin level of ≥ 3.0 g/dL or requiring transfusion of ≥ 3 units of whole blood or packed RBCs AND does not meet the criteria of life-threatening or extensive bleeding. **III. Extensive** Bleeding meeting either of the following: • Overt source of bleeding with drop in hemoglobin of ≥ 4 g/dL or whole blood or packed RBC transfusion ≥ 4 U within any 24-h period • Bleeding with drop in hemoglobin 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 meeting either of the following: • 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. † "Overt" bleeding is defined as clinically obvious bleeding (visible bleeding and bleeding seen only by imaging). Examples of overt bleeding include: • Pseudoaneurysm

<table>
<tr><td>Term</td><td>Definition</td></tr>
<tr><td></td><td>

Retroperitoneal hematoma seen on CAT scan
Visible access site hematoma
Gross hematuria, hematemesis and hematochezia

Procedural bleeding has to be an overt bleeding from a vascular system either at or remote from the access/surgical site. Thresholds for reporting procedural bleeding for study index procedure >100 ml total EBL (Estimated Blood Loss) from access site.
All post-procedural overt bleeding events must be reported including hematuria, melena, hematemesis, occult gastrointestinal bleeds or drop in Hgb with overt source of bleeding detected requiring transfusions etc. If the reason for Hgb drop was other than due to the overt bleeding i.e. due to hemodilution, chronic iron deficiency anemia etc., it will not be considered as a bleeding event.

Severe Bleeding
See the section of severe bleeding below.
</td></tr>
<tr><td>Causality Assessment</td><td>
Adverse events will be assessed by the investigator, etc. for causality to the study device and index procedure. The relationship between the use of the study device and study/implant procedure and the occurrence of each adverse event shall be assessed and categorized. During causality assessment, clinical judgement shall be used and the relevant study documents (i.e. Clinical Protocol, ICF, IFU and/or IB) shall be consulted for the listing of foreseeable adverse events/potential risks. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illnesses or risk factors shall also be considered
<table>
<tr><td></td><td>Category</td><td>Definition</td></tr>
<tr><td>1</td><td>Related</td><td>
The serious event is associated with the devices used in the clinical study and study procedure beyond reasonable doubt when:

the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
The event has a temporal relationship with investigational device use/ application or procedures;
The event involves a body-site or organ that:

the investigational device or procedures are applied to;
the investigational device or procedures are applied to;

the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
harm to the patient is due to error in use;
the event is attributable to diagnostic error by the diagnostic device used in the clinical study (if applicable);

In order to establish relatedness, not all criteria listed above must be met at the same time, depending on the type of device, procedure and the serious event.
</td></tr>
<tr><td>2</td><td>Probable</td><td>

The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably [be] explained by another cause, but additional information may be obtained.

</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Term</td><td colspan="3">Definition</td></tr>
<tr><td></td><td>3</td><td>Possible</td><td>• the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.</td></tr>
<tr><td></td><td>4</td><td>Unlikely</td><td>• the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.</td></tr>
<tr><td></td><td>5</td><td>Not related</td><td>Relationship to the devices or procedures can be excluded when:
• the event is not a known side effect of the product category the device belongs to or of a similar device and procedure
• the event has no temporal relationship with the use of the investigational device or the procedures
• the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible
• the discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
• the event involves a body-site or an organ not expected to be affected by the device or procedure
• the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors)
• the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
• harms to the patient are not clearly due to use error
In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.</td></tr>
<tr><td></td><td colspan="3">An adverse event can be related both to the study procedure and the device.

Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use/application.
In some particular cases the event may not be able to be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigatoror sub-investigator(s) will make the maximum effort to define and categorize the event and avoid these situations.</td></tr>
<tr><td>Frailty Scale©
Clinical Frailty Scale</td><td colspan="3">A 9 point single question administered to measure frailty. Developed by the Canadian Study of Health and Aging (CSHA).</td></tr>
<tr><td>Death
(MVARC[60])</td><td colspan="3">I. Cardiovascular death
Cardiovascular death is defined as any of the following contributing conditions:
• Heart failure (sub-classified into left ventricular vs. right ventricular dysfunction)
• Myocardial infarction</td></tr>
</table>

Term	Definition
	• 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) **II. Non-cardiovascular death** 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 causes
Device Deficiency	A device deficiency is defined as an unfavorable condition broadly related to the quality, safety, performance, etc. of the investigational device used in the clinical study, including breakage and malfunction, whether it occurs in any of the stages of design, delivery, storage, or use. Reference: MDR2017 defines a device deficiency as "any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer."
[redacted]	[redacted]
Device Malfunction (ISO 14155 Definition)	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use.
[redacted]	[redacted]
[redacted]	[redacted]
Device Time	Time from delivery system insertion to delivery system removal.
Durable Right Ventricular Assist Device (RVAD) Implantation	Implantation of a right ventricular assist device intended as a bridge to heart transplantation or as a long-term destination therapy.

Term	Definition
[redacted]	[redacted]
Enrollment	A subject is considered enrolled in this trial when the index procedure is performed at the time when invasion such as puncture or skin incision at the access site is started for introduction of the study device.
EQ-5D-5L	A survey comprised of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that measures health-related QOL.
Explant	Removal of the investigational device after completion of the implant procedure for any reason.
[redacted]	[redacted]
Hemolysis (MVARC [60])	The presence of a paravalvular leak on transesophageal or transthoracic echocardiography plus anemia requiring transfusion plus increased haptoglobin and/or LDH levels.
Hospitalization/Re-hospitalization (MVARC[60])	Hospitalization is defined as an unplanned admission to the hospital, including an emergency department stay, for the purpose of diagnosis or treatment after discharge from the hospitalization for the study procedure. All hospitalizations will be classified according to the following criteria: • **Congestive heart failure (CHF) hospitalization** Hospitalization for ≥ 24 h with symptoms and/or laboratory evidence of worsening heart failure, in which intravenous or mechanical heart failure therapies are administered. An emergency room stay for ≥ 24 h would qualify as a CHF hospitalization endpoint, even absent formal hospital admission, as such a prolonged stay represents a severe episode of heart failure • **Other cardiovascular hospitalization** 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 • **Noncardiovascular hospitalization** Hospitalization not due to heart failure or other cardiovascular causes, as defined above Patients hospitalized with heart failure meeting these criteria should further be subclassified as follows: • **Primary (cardiac-related) heart failure** Due to any cardiac cause, including primary LV dysfunction with or without medication or dietary noncompliance, acute myocardial infarction (MI), arrhythmias, and worsening valve dysfunction. • **Secondary (noncardiac-related) heart failure** When a noncardiac primary condition is present such as pneumonia, urinary tract infection, or renal failure, which results in fluid overload or myocardial failure. Note: Only primary heart failure should be considered a valid criterion for heart failure hospitalization.
Kansas City Cardiomyopathy Questionnaire (KCCQ)	Health-related QOL measure for patients with congestive heart failure
Katz Index Katz Index of Independence in Activities of Daily Living	Completed by the site, the Katz ADL is a 6-question assessment of functional status as a measurement of the patient's ability to perform activities of daily living
Local Heart Team	"Local Heart Team" for the purpose of this study, must include a minimum of 1 Cardiologist, 1 Cardiac Surgeon, 1 Heart Failure specialist, and 1 echocardiographer.
Length of Stay	Number of days from the index procedure to discharge
Major Adverse Event (MAE)	In this trial, MAEs are defined as Cardiovascular mortality, Myocardial infarction, Stroke, New need for renal replacement therapy, Severe bleeding(fatal, life-threatening, extensive, or major bleeding, as defined by

Term	Definition
	MVARC), non-elective tricuspid valve re-intervention (percutaneous or surgical), major access site and vascular complications, major cardiac structural complications due to access-related issues, device-related pulmonary embolism, arrhythmia and conduction disorder requiring permanent pacing
Major device fracture (MVARC[60])	A break, tear, perforation, or other structural defect in the device (stent, housing, leaflet, arm, and so on) resulting in device failure, resulting in recurrent symptoms, or requiring reintervention
Modified Rankin Scale (mRS)	0: No symptoms at all 1: No significant disability, despite symptoms; able to carry out all usual duties and activities 2: Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance 3: Moderate disability; requiring some help, but able to walk without assistance 4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6: Dead
Myocardial Infarction (MVARC[60])	**I. Periprocedural MI (≤ 48 h after the index procedure)*†** A. In patients with normal baseline CK-MB (or troponin): • The peak CK-MB measured within 48 h of the procedure rises to ≥10x the local laboratory ULN (Upper Limit of Normal) 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 (left bundle branch block) LBBB, OR • In the absence of CK-MB measurements and a normal baseline troponin, a troponin (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 mm in ≥2 contiguous leads (measured 80 ms after the J-point), or to ≥35x ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB. B. In patients with elevated baseline CK-MB (or troponin): • The CK-MB (or troponin) 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 troponin) 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 ischemia B. ECG changes indicative of new ischemia (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 ischemia, 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‡** Notes: The use of high sensitivity (hs)-troponins is recommended for diagnosis of type II (spontaneous) MI, but has not been studied for assessment of periprocedural MI. Standard troponin assays are therefore recommended for evaluation of type I MI. Situations where MI is suspected must be carefully evaluated by taking into

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td></td><td>consideration past medical history, procedural specifics, renal function etc. It is known that cardiac procedures are associated with multiple confounding factors that contribute to myocardial damage.

* Periprocedural biomarker elevation >ULN not meeting the criteria for MI should be categorized as “myonecrosis not meeting MI criteria.”
†Adapted from Moussa et al.[85]
‡Adapted with permission from Thygesen et al.[66]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>NYHA Functional Class
New York Heart Association Classification (NYHA)[30]</td><td><NYHA Functional Class>
<table><tr><td>Class I</td><td>Patients with cardiac disease but without resulting limitation of physical activity.
Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.</td></tr><tr><td>Class II</td><td>Patients with cardiac disease resulting in slight or moderate limitation of physical activity. They are comfortable at rest.
Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.</td></tr><tr><td>Class III</td><td>Patients with marked limitation of physical activity. They are comfortable at rest.
Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.</td></tr><tr><td>Class IV</td><td>Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort.
Symptoms of heart failure or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td></tr></table></td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Pulmonary Embolism
(Sponsor Definition)</td><td>Pulmonary embolic event is an operative, autopsy or clinically documented embolus that produces symptoms from complete or partial obstruction of a pulmonary or bronchial artery. Confirmation of pulmonary embolism is done through diagnostic testing such as TTE/TEE, ventilation/perfusion lung (VQ) scan, angiogram, MRI or CT.</td></tr>
<tr><td>Re-intervention</td><td>Any surgical or percutaneous intervention that repairs, alters or adjusts, or replaces the previously implanted investigational device or native valve after the patient leaves the procedure room (the catheterization laboratory/operating room) from index procedure.
Notes:
The endpoint is “non-elective tricuspid valve re-intervention (percutaneous or surgical)”

Elective: The procedure could be deferred without increased risk of compromised cardiac outcome
Non- The procedure could not be deferred without increased risk of</td></tr>
</table>

Term	Definition
	elective: compromised cardiac outcome; includes Urgent and Emergent: • Urgent – Procedure required during same hospitalization in order to minimize chance of further clinical deterioration. • Emergent – An emergency operation is one in which there should be no delay in providing operative intervention.
[redacted]	[redacted]
Serious Adverse Events (SAE) (Japan- GCP)	A serious adverse event is an event meeting any of the following conditions that occurs in a subject of the clinical study, regardless of the causal relationship with the devices used in the clinical study, according to Article 274, Paragraph 2 of Enforcement Regulations of the Japanese Pharmaceutical Affairs Law: a. A case of death b. A case that may lead to death c. A case that requires hospitalization in a medical institution or extension of a hospitalization period for treatment d. A case of disability e. A case that may lead to disability f. A case of a serious disease according to cases listed in a. through e. of the preceding item g. A congenital disease or abnormality in later generations However, occurrence of a new adverse event or hospitalization which is not accompanied by exacerbation of pre-operative complications, like the examples shown below, will not be regarded as a serious adverse event and will not require reporting to the sponsor. - Hospitalization for the treatment planned in the pre-procedure period (e.g. hospitalization for a surgery for the pre-operative complication that has become possible after improvement of the heart condition [e.g. cancer surgery], elective PCI) - Hospitalization for management (e.g. periodical health check-up, hospitalization for tests, educational hospitalization) - Admission to a rehabilitation institution
[redacted]	[redacted]
SF-36v2	A survey with 36 questions that results in two scales of mental and physical functioning and overall health related quality of life. In Japan, three scales of mental, physical, and role/social component summary score may be used. SF-12v2: A 12 question abridged and validated version of the SF-36v2
Stroke and TIA (MVARC[60])	**Stroke Diagnostic Criteria** I. Acute episode of a focal or global neurological deficit with at least one of the following: A. Change in the level of consciousness B. Hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body C. Dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke II. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with a neurologist*. **The neurological event type classification** I. Stroke: Duration of symptom: • Duration of a focal or global neurological deficit ≥ 24 hours or • Duration of a focal or global neurological deficit < 24 hours if available

Term	Definition
	neuroimaging indicates a new intracranial or subarachnoid hemorrhage (hemorrhagic stroke) or central nervous system infarction (ischemic stroke) • The neurological deficit results in death II. Transient ischemic attack (TIA) : Duration of a focal or global neurological deficit < 24 hours and neuroimaging does not demonstrate a new hemorrhage or infarct **Confirmation of the diagnosis by at least one of the following** I. Neurologist or neurosurgical specialist, or II. Neuroimaging procedure (CT or brain MRI) III. Non-neurologist physician (if neurologist is not available) IV. Clinical presentation alone*** **Stroke types will be adjudicated as:** Ischemic: an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of the central nervous system tissue Hemorrhagic: an acute vascular episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage Undetermined: if there is insufficient information to allow categorization as ischemic or hemorrhagic **Stroke severity** It is recognized that an assessment of stroke is incomplete without an appropriate measurement of the disability resulting from the stroke, hence, mRS closest to 90 days post event** will be used to assess clinical disability. I. **Disabling stroke** mRS score of ≥ 2 at 90 days (or the last available clinical visit with evaluable data) AND an increase in ≥ 1 mRS category from an individual's pre-stroke baseline II. **Non-disabling stroke** mRS score of < 2 at 90 days (or the last available clinical visit with evaluable data) AND an increase in ≥ 1 mRS category from an individual's pre-stroke baseline **Transient ischemic attack (TIA)** Acute episode of a focal or global neurological deficit fulfilling the following criteria: I. Resulting in at least one of the following: • Change in the level of consciousness • Hemiplegia • Hemiparesis • Numbness • Sensory loss affecting one side of the body • Dysphasia or aphasia • Hemianopia • Amaurosis fugax • Other neurological signs or symptoms consistent with stroke II. Duration of deficit could be one of the following: • A focal or global neurological deficit < 24 hours • Any available neuroimaging does not demonstrate a new hemorrhage or infarct III. No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with a neurologist* Notes: *, Patients with nonfocal global encephalopathy will not be reported as a

Term	Definition
	stroke without unequivocal evidence based upon neuroimaging studies **, Evaluation of stroke between 30 and 90 days is acceptable if 90-day follow-up not available ***, Evaluation of stroke between 30 and 90 days is acceptable if 90-day follow-up not available.
[redacted]	[redacted]
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity of outcome has not been identified in the current version of the risk analysis report Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity of outcome has been identified in the risk analysis report.
6-Minute Walk Test	A submaximal exercise test used to assess aerobic capacity and endurance that entails measurement of distance walked over a span of 6 minutes.

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