TRISCEND JAPAN (2021-12)

Statistical Analysis Plan

Study Title:	Edwards EWJ-202 Transcatheter Tricuspid Valve Replacement System: Investigation of Safety and Clinical Efficacy using a Novel Device in patient with at least severe tricuspid regurgitation in JAPAN
Study Number:	2021-12
Protocol Version:	[redacted]
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Glossary of Terms

ABBREVIATION	DEFINITION OR DESCRIPTION
6MWT	6-Minute Walk Test
6MWD	6-Minute Walk Distance
ADL	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
AT	As Treated
BNP	Human Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CSC	Central Screening Committee
CSHA	Canadian Study of Health and Aging
CSR	Clinical Study Report
CRT	Cardiac Resynchronization Therapy
CV	Cardiovascular
DD	Device Deficiency
ECG	Electrocardiogram
ECL	Echo Core Lab
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FCS	Fully Conditional Specification
GGT	Gamma-Glutamyl Transferase
HFH	Heart Failure Hospitalization
HLGT	High Level Group Term
ICD	Implantable Cardioverter-Defibrillator
ITT	Intention-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left Ventricular Ejection Fraction
LOS	Length of Stay
MAE	Major Adverse Event
MI	Myocardial Infarction
MVARC	Mitral Valve Academic Research Consortium
NYHA	New York Heart Association
OR	Operating Room
PP	Per-protocol

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ABBREVIATION	DEFINITION OR DESCRIPTION
PPM	Permanent Pacemaker
PT	Preferred Term
RVAD	Right Ventricular Assist Device
SAP	Statistical Analysis Plan
SD	Standard Deviation
SLDA	Single Leaflet Device Attachment
SOC	System Organ Class
STS	Society of Thoracic Surgery
TEE	Transesophageal Echocardiography
TR	Tricuspid Regurgitation
TTE	Transthoracic Echocardiography
TV	Tricuspid Valve

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1. INTRODUCTION

This statistical analysis plan (SAP) specifies the statistical methods to be implemented for the analysis of data collected within the scope for the Edwards Lifesciences' Protocol 2021-12 [redacted]. Edwards EWJ-202 Transcatheter Tricuspid Valve Replacement System: Investigation of Safety and Clinical Efficacy using a Novel Device in patients with at least severe tricuspid regurgitation in JAPAN. This SAP provides detailed instructions as to how each analysis will be performed.

Results obtained from the analyses specified in the SAP will become the basis of clinical study reports (CSR) for this protocol. Any deviations from the final approved SAP will be documented in the CSR.

2. STUDY DESIGN

2.1 Study Objectives

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.

2.2 Overall Study Design and Plan

This is 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.

2.2.1 Main (Primary) Cohort

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 described in section 2.2.2). Up to 8 sites were selected from the perspective of ensuring the study quality and feasibility.

2.2.2 Roll-in Cohort

This trial incorporates a roll-in cohort to provide operators with 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]

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 the results may be presented as reference information in Clinical Study Report (CSR).

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2.2.3 Planned Trial Period

[redacted]

2.2.4 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.

2.3 Sample Size Consideration

The roll-in cohort will include a maximum of three patients per site (e.g., if 8 sites used, a maximum of 24 roll-in patients).

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

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2.3.1 All-cause Mortality

[redacted]

2.3.2 Heart Failure Hospitalization

[redacted]

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[redacted]

3. STUDY ENDPOINTS

3.1 Primary Endpoints (Co-primary)

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

3.2 Secondary Endpoints

3.2.1 Secondary Effectiveness Endpoints

Following are the secondary effectiveness endpoints evaluated at timepoints specified in the parentheses:

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

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

(3) Quality of Life (QOL) questionnaires (30 days, 6 months, 1 year, 2 years)

- Short Form 36-item Health Survey (SF-36)
- The Kansas City Cardiomyopathy Questionnaire (KCCQ)
- EuroQol – 5 Dimension – 5 Level (EQ-5D-5L)

(4) 6-Minute Walk Distance (6MWD) (30 days, 6 months, 1 year, 2 years)

3.2.2 Secondary Safety Endpoints

Following are the secondary safety endpoints evaluated at timepoints specified in the parentheses:

(1) Composite endpoint of Major Adverse Events (MAEs) (30 days):

- Cardiovascular mortality
- Myocardial infarction
- Stroke
- New need for renal therapy
- Severe bleeding (fatal, life-threatening, extensive, or major bleeding as defined by Mitral Valve Academic Research Consortium (MVARC))
- Non-elective tricuspid valve re-intervention (percutaneous or surgical)
- Major access site and vascular complications

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- 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)

3.3 Exploratory Endpoints

[redacted]

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[redacted]

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3.4 Additional Outcomes

[redacted]

3.4.2 [redacted]

[redacted]

3.4.3 [redacted]

[redacted]

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4. 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]

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[redacted]

In principle, the Roll-in cohort will be analyzed independently from the main cohort but may be pooled with the Enrolled Population – Safety / Effectiveness (or the AT Population etc., depending on the endpoints) and analyzed for reference information.

5. DEFINITIONS

5.1 Analysis Dates and Days

- **Reference Start Date and Day 0**

  The reference start date is defined to be the date of the index procedure. The index procedure date is defined on the day the first skin incision for the study device is documented. If a patient has multiple procedure forms, the procedure form with the first documented skin incision for study device will be used. If no form has a skin incision for the study device documented, then the procedure information corresponding to the date of the first procedure will be used.

  The reference start date will be Day 0.

- **Last Participation Date**

  The Last Participation Date is defined as the last date the patient was seen (refer to the programming convention for complete details).

- **Last Participation Day**

  Last Participation Day = Last Participation Date – Reference Start Date

  Note: Last Participation Day is used as the censor day for Kaplan-Meier analysis.

- **Study Day**

  Study Day = Date – Reference Start Date

5.2 Analysis Windows

An assessment is considered scheduled if the assessment is identified by a nominal visit name (e.g., “Discharge”, “30 day”, and “1 year”) regardless if the actual visit date is within the protocol defined visit window. An assessment is considered unscheduled if no nominal visit name is identified. Unless specified, measurements collected from unscheduled assessments should be excluded from analyses.

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6. DATA AND ANALYSIS CONVENTIONS

6.1 General Conventions

Data will be analyzed according to the cohorts: (a) roll-in patients, (b) main cohort patients

Descriptive summaries will follow the conventions below.

- 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.
- 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.
- Descriptive statistics will be calculated in each observation period, and the changes from baseline to each observation period will also be calculated.
- 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."
- 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.
- 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.
- 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.
- All analyses will be performed using SAS version 9.4 or the latest release version at the time of analysis unless otherwise specified.

6.2 Quality of Life Questionnaires

Quality of life questionnaires will be scored according to algorithms provided by the vendor. The various summary scores produced by the algorithms will be analyzed as continuous variables.

6.3 General Specifications

- Unless otherwise specified, confidence intervals will be two sided, using alpha = 0.05.
- Unless otherwise specified, the precise form of each algorithm will be the default of SAS, using the latest release installed at Edwards at the time of analysis.

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6.4 Handling of Missing Data

In principle, 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.



For missing data due to patient withdrawal or lost to follow-up in the analyses of time-dependent endpoints, the patients will be censored on the last participation date as defined in section 5.1.

Unless otherwise specified, all statistical analyses will be performed using only those patients with available data required for endpoint analysis, and no other missing value imputation will be performed.

7. SUMMARY OF BASELINE INFORMATION

7.1 Patient Enrollment and Accountability

The number of enrolled patients will be summarized by investigational site for the enrolled Population – Safety. The table will be sorted by enrollment going from the highest enrollment site to the lowest enrollment site.

The summary of patient disposition will include numbers of enrolled patients who were alive and in study, who died, and who discontinued the study by follow-up visits for Enrolled Population - Safety, Enrolled Population - Effectiveness, AT Population, and PP Population.

Similar enrollment and patient disposition tables will also be generated for the roll-in cohort for Enrolled Population – Safety.

7.2 Demographics and Baseline Characteristics

Descriptive summary statistics of demographics and baseline characteristics (including baseline risk assessments) will be provided using the Enrolled Population – Safety, Enrolled Population – Effectiveness, AT Population for main cohort; and using the Enrolled Population – Safety, Enrolled Population – Effectiveness, and AT Population for roll-in cohort.

7.3 Medical History and Prior Intervention

Medical history and prior interventions grouped by event types (cardiovascular, non-cardiovascular, and cardiovascular intervention or surgeries) will be summarized by counts and percentages. For both cohorts, Enrolled Population – Safety, Enrolled Population – Effectiveness, and AT Population will be used.

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7.4 Baseline Risk Assessments

As outlined in section 7.2.

7.5 Procedural Information

Procedural information will be summarized including but not limited to the type of anesthesia, procedure duration, implanted valves using Enrolled Population – Safety for both cohorts. The length of stay for the index hospitalization will be summarized using AT Population for both cohorts.

8. STATISTICAL ANALYSIS OF STUDY ENDPOINTS

8.1 Primary Endpoints

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

Primary analysis will be performed for all-cause mortality and heart failure hospitalization individually, and descriptive statistics of all-cause mortality and heart failure hospitalization at 1 year after the procedure will be provided. [redacted]

All-cause mortality and heart failure hospitalization rates at 1 year after the procedure and corresponding 95% confidence intervals will be computed using the Kaplan-Meier estimate with the standard errors being computed using Greenwood's formula for Enrolled Population – Safety if needed.

For all-cause mortality endpoint, patients who are alive will be censored on their data cut-off date. Patients who withdraw from the trial and are alive will be censored on the date of withdrawal.

For heart failure hospitalization endpoint, patients who do not experience any heart failure hospitalizations will be censored on their data cut-off date. Patients who die will be censored on the date of death. Patients who withdraw from the trial without a hospitalization will be censored on the date of withdrawal.

8.2 Secondary Endpoints

8.2.1 Effectiveness

The secondary effectiveness endpoints of the study are as follows:

- TR grade at 30 days, 6 months, 1 year, and annually until 5 years
- NYHA functional class at 30 days, 6 months, 1 year, and annually until 5 years
- QOL (SF-36, KCCQ and EQ-5D-5L) at 30 days, 6 months, 1 year, and 2 years
- 6MWD at 30 days, 6 months, 1 year, and 2 years

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For each secondary effectiveness endpoints, descriptive statistics will be calculated at each pre-specified follow-up period using Enrolled Population – Effectiveness for roll-in and main cohort, separately. The change from baseline to each observation period will be presented in the same way.

The distribution (numbers of patients and percentages) in the various NYHA classes and TR grade will be tabulated at baseline, 30 days, 6 months, 1 year, and annually up to 5 years. Changes from baseline in TR grade assessed by Echo Core Lab and NYHA function class will also be presented as "paired". Change from baseline in NYHA Functional Classification will be presented as shift from baseline for each of the pre-specified follow-up periods. Patients that are missing a baseline or follow-up values will be excluded from the paired analysis for the Enrolled Population – Effectiveness.

Descriptive statistics in the QOL (SF-36, KCCQ and EQ-5D-5L) and 6MWD will be calculated at baseline, 30 days, 6 months, 1 year and 2 years. Change from baseline will be summarized by mean and standard deviation. Patients that are missing a baseline or follow up values will be excluded from the analysis.

8.2.2 Safety

All the secondary safety endpoints will be performed for the Enrolled Population – Safety of roll-in and main cohort, separately.

For the composite of major adverse event (MAE), descriptive statistics such as the number of patients with event, the number of events, event rate at 30 days will be calculated. In addition, the composite of MAE rate at 30 days will be computed using the Kaplan-Meier method with the standard errors being computed using Greenwood’s formula.

For rates of each individual component of composite MAEs, all-cause mortality rate, all-cause hospitalization rate, durable RVAD implantation or heart transplant rate, tricuspid valve surgery or percutaneous tricuspid intervention rate, and paracentesis rate at 30 days, 6 months, 1 year and annually thereafter and corresponding 95% confidence intervals will be computed using the Kaplan-Meier method with the standard errors being computed using Greenwood’s formula.

For the number of heart failure hospitalization, descriptive statistics such as the number of patients with events, the number of events, the total follow-up time (in patient-years), and the annualized rate will be calculated. In addition, the 95% confidence interval using Poisson distribution for the annualized rate will be computed.

8.3 Exploratory Endpoints



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The primary analysis population for these endpoints will be Enrolled Population – Effectiveness.

8.4 Additional Outcomes

The following additional outcomes will be analyzed separately for both cohorts, as applicable.

8.4.1 [redacted]

[redacted]

8.4.2 [redacted]

[redacted]

8.4.3 [redacted]

[redacted]

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[redacted]

8.5 [redacted]

[redacted]

9. ANALYSIS OF SAFETY

9.1 Deaths

The primary cause of death will be summarized descriptively by counts and percentages at 30 days and 1 year for both cohorts. No statistical testing will be performed. All deaths will be listed.

9.2 Adverse Events (AEs)

A summary of the percentage of patients who experience an early adverse event (≤ 30-day post-procedure) and late adverse event (> 30 days post- procedure) will be reported for all adverse events, device-related and procedure-related adverse events, and serious adverse events.

In addition, all AEs and SAEs with onset on or after the Day 0 as described above will be summarized with MedDRA codes (System Organ Class (SOC) and Preferred Term (PT)) by early events (≤ 30 days) and late events (> 30 days) for Enrolled Population – Safety.

9.3 Device Deficiency

All device deficiencies for both cohorts on or after the Day 0 including but not limited to time of occurrence, device component failed, device model number and if AE occurred will be summarized and listed for Enrolled Population – Safety.

10. CHANGES FROM PROTOCOL SPECIFIED ANALYSES

NA

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12. APPENDIX

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