A Clinical Trial of Transcatheter Aortic Valves in Dialysis Patients (Japan)

NCT02903420

January 6, 2020

**PROTOCOL**

**A Clinical Trial for Transcatheter Aortic Valve Implantation in Chronic Dialysis Patients with Aortic Valve Stenosis**

**Study Device ID Code: EWJ-003**

Sponsor
Edwards Lifesciences Corporation

| | |
|---|---|
| Clinical Protocol ID Code: | EW-P-003 |
| Edition number: | Ver. 6.2 |
| Date of creation: | January 6, 2020 |





This clinical trial will be conducted in compliance with "Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices" (Act No. 145 of 1960, hereinafter referred to as "PMD Act"), ethical principles that have their origin in the Declaration of Helsinki, the Japan Ministerial Ordinance on Good Clinical Practice for Medical Devices (Ordinance of the Ministry of Health, Labour and Welfare No. 36 of 2005, hereinafter referred to as "J-GCP"), ministerial ordinances partially amending J-GCP and the relating regulations, and this protocol.

List of abbreviations

| Abbreviation | English |
|---|---|
| AATS | American Association for Thoracic Surgery |
| ACC | American College of Cardiology |
| ACE-I | Angiotensin Converting Enzyme Inhibitor |
| ACT | Activated Clotting Time |
| AHA | American Heart Association |
| ALT | Alanine Aminotransferase |
| ARB | Angiotensin II Receptor Blocker |
| AS | Aortic Stenosis |
| ASE | American Society of Echocardiography |
| AST | Asparate Aminotransferase |
| AT | As-Treated |
| BARC | Bleeding Academic Research Consortium |
| BMI | Body Mass Index |
| BSA | Body Surface Area |
| CCB | Calcium Channel Blocker |
| CCS | Canadian Cardiovascular Society |
| CEC | Clinical Event Committee |
| CFR | Code of Federal Regulation |
| CK | Creatine Kinase |
| CKD | Chronic Kidney Disease |
| CK-MB | Creatine Kinase MB Isoenzyme |
| CRP | C-reactive Protein |
| CT | Computed Tomography |
| DMC | Data Monitoring Committee |
| e-CRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| eGFR | Estimated Glomerular Filtration Rate |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GOT | Glutamic Oxaloacetic Transaminase |
| GPT | Glutamic Pyruvate Transaminase |
| HMG-CoA | 3-Hydroxy-3-methylglutaryl-coenzyme A |
| ICU | Intensive Care Unit |
| IDE | Investigational Device Exemption |
| ISO | International Organization for Standardization |
| ITT | Intention-to-treat |
| LBBB | Left Bundle-branch Block |
| LDH | Lactate Dehydrogenase |
| LVOT | Left Ventricular Outflow Tract |
| MACCE | Major Adverse Cardiac and Cerebro-Vascular Events |
| MRI | Magnetic Resonance Imaging |
| NIHSS | National Institutes of Health |
| NYHA | New York Heart Association |
| PCI | Percutaneous Coronary Intervention |
| PET | Polyethylene Terephthalate |
| PG | Performance Goal |
| QOL | Quality of Life |
| sAVR | Surgical Aortic Valve Replacement |
| SF-12 | Short Form 12-item Health Survey |
| STS | Society of Thoracic Surgeons |
| TA | Transapical |

| Abbreviation | English |
|---|---|
| TAo | Transaortic |
| TAVI | Transcatheter Aortic Valve Implantation |
| TEE | Transesophageal Echocardiography |
| TF | Tranfemoral |
| URL | Upper Range Limit |
| VARC | Valve Academic Research Consortium |
| VI | Valve Implant |

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## PROTOCOL SYNOPSIS

Study Title: A Clinical Trial for Transcatheter Aortic Valve Implantation in Chronic Dialysis Patients with Aortic Valve Stenosis
Study Device ID Code: EWJ-003
Clinical Protocol ID Code: EW-P-003

<table>
<tr><th>Item</th><th>Content</th></tr>
<tr><td>Study Objective</td><td>The study objective of this trial is to evaluate safety and effectiveness of Edwards SAPIEN 3 Transcatheter Heart Valve System in the treatment of symptomatic severe aortic stenosis patients on chronic dialysis, who are determined by the heart team to be unable to undergo safe open surgical therapy and have the benefits of the study valve implantation.</td></tr>
<tr><td>Study Design</td><td>A single arm, prospective, open, non-randomized, Japanese multicenter study</td></tr>
<tr><td>Study Device</td><td>Edwards SAPIEN 3 Transcatheter Heart Valve System (EWJ-003)<br>• Transcatheter heart valve (THV) (Size: 20, 23, 26, 29 mm)<br>• Delivery system (transfemoral approach)<br>○ Delivery system<br>○ Introducer sheath set<br>○ Balloon catheter<br>• Delivery system (transapical/transaortic approach)<br>○ Delivery system<br>○ Introducer sheath set<br>○ Balloon catheter<br>• Other components<br>○ Crimper<br>○ Crimping accessory<br>○ Inflation device/inflation syringe<br><THV Sizes of the Investigational Device Available for the Trial><br>
<table>
<tr><th rowspan="2">Native Annulus Size (TEE)</th><th colspan="2">Native Annulus Size (CT)</th><th rowspan="2">THV Size</th><th rowspan="2">Valve Height</th></tr>
<tr><th>Native Annulus Area</th><th>Area-derived Diameter</th></tr>
<tr><td>16 - 19 mm</td><td>273 - 345 mm$^2$</td><td>18.6 - 21.0 mm</td><td>20 mm</td><td>15.5 mm</td></tr>
<tr><td>18 - 22 mm</td><td>338 - 430 mm$^2$</td><td>20.7 - 23.4 mm</td><td>23 mm</td><td>18 mm</td></tr>
<tr><td>21 - 25 mm</td><td>430 - 546 mm$^2$</td><td>23.4 - 26.4 mm</td><td>26 mm</td><td>20 mm</td></tr>
<tr><td>24 - 28 mm</td><td>540 - 683 mm$^2$</td><td>26.2 - 29.5 mm</td><td>29 mm</td><td>22.5 mm</td></tr>
</table></td></tr>
<tr><td>Access Approach</td><td>Transfemoral (TF), transapical (TA) or transaortic (TAo) approach</td></tr>
<tr><td>Patient Population</td><td>Chronic dialysis patients with symptomatic severe aortic stenosis, who are</td></tr>
</table>

| Item | Content |
|---|---|
| | judged by the heart team to be unable to undergo safe open surgical therapy and have the benefits of the study valve implantation. |
| Inclusion Criteria | 1. Patients determined by the heart team to be unable to undergo safe open surgical therapy and have the benefits of the study valve implantation. Specifically, considering the followings as risk factors, the risk should be comprehensively determined.<br>• Porcelain aorta<br>• History of mediastinal radiotherapy<br>• History of mediastinitis<br>• Remarkable thoracic deformity<br>• Previous open heart surgery or coronary-artery bypass grafting (CABG)<br>• Chronic obstructive pulmonary disease<br>2. Patient has senile degenerative aortic valve stenosis (AS) with one of the following echocardiographic criteria. Measurement of aortic valve area (AVA) at baseline must be acquired within 60 days prior to the study procedure .<br>(a) Mean pressure gradient ≥ 40 mmHg<br>(b) Aortic flow velocity ≥ 4.0 m/s<br>(c) AVA at baseline ≤ 1.0 $cm^2$<br>(d) AVA index ≤ 0.6 $cm^2/m^2$<br>3. Patient has symptoms associated with AS ≥ NYHA class II.<br>4. The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.<br>5. The subject and the investigator agreed to comply with all required post-procedural follow-up visits.<br>6. Patient has been on dialysis (hemodialysis or peritoneal dialysis) in stable condition for ≥ 3 months.<br>7. Patient has any one of the following native aortic valve annulus sizes as measured by transesophageal echocardiography (TEE) or 3D-computed tomography (CT).<br>(a) Native annulus size ≥ 16 mm and ≤ 28 mm by TEE<br>(b) Native annulus area ≥ 273 $mm^2$ and ≤ 683 $mm^2$ by 3D-CT<br>(c) Area-derived diameter ≥ 18.6 mm and ≤ 29.5 mm by 3D-CT<br>8. Patient is verified by the Case Review Process that the treatment with EWJ-003 will likely benefit the patient. |
| Exclusion Criteria | 1. Patient has an evidence of an acute myocardial infarction (MI) within 1 month (30 days) prior to the study procedure . Acute MI is defined as; Q |





| Item | Content |
|---|---|
| | wave MI, or non-Q-wave MI with elevation of creatine kinase MB isoenzyme (CK-MB) or troponin, together with the evidence of myocardial ischemia with at least one of the following findings:<br>• Symptoms of ischemia<br>• Electrocardiogram (ECG) changes indicative of new ischemia (ST-T changes, left bundle-branch block [LBBB])<br>• Imaging evidence of a new loss of viable myocardium or new wall motion abnormality.<br>2. Patient has a congenital unicuspid or bicuspid aortic valve, or a non-calcified aortic valve.<br>3. Patient has severe aortic valve regurgitation.<br>4. Patient has severe mitral valve regurgitation.<br>5. Patient has an evidence of any therapeutic invasive cardiac procedures within 30 days prior to the study procedure . However, implantation of a permanent pacemaker or balloon valvuloplasty for bridging to procedure after a qualifying echocardiography are excluded.<br>6. Patient with planned concomitant surgical or transcatheter ablation for atrial fibrillation.<br>7. Patient has pre-existing prosthetic valve in any position.<br>8. Patient is at a high risk of bleeding, difficult to have appropriate treatment, or unable to receive appropriate anticoagulation or antiplatelet therapy.<br>• Leukopenia (white blood cell < 3,000 cells/$mm^3$)<br>• Thrombocytopenia (platelet < 50,000 cells/$mm^3$)<br>• Bleeding diathesis or coagulopathy<br>• Active gastro-intestinal ulceration, or upper gastro-intestinal bleeding within the past 3 months<br>• Refuse blood transfusion<br>• Receiving anticoagulant and/or antiplatelet medication unable to interrupt for the study procedure<br>• Concluded by investigator that appropriate anticoagulation or antiplatelet therapy is difficult for any other reasons<br>9. Patient has untreated clinically significant coronary artery disease requiring revascularization.<br>10. Patient has hemodynamic instability requiring inotropic support or mechanical heart assistance. Patient has respiratory instability requiring mechanical ventilation.<br>11. Patient requires an emergency surgery for any reason. |





| Item | Content |
|---|---|
| | 12. Patient has hypertrophic cardiomyopathy with or without obstruction.<br>13. Patient has severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20%.<br>14. Patient has echocardiographic evidence of intracardiac mass, thrombus, or vegetation.<br>15. Patient has hypersensitivity to or a known contraindication of heparin and/or aspirin, which cannot be adequately pre-medicated. Patient has a known hypersensitivity to contrast media.<br>16. Patient has hypersensitivities to cobalt, chromium, nickel, molybdenum, titanium, manganese, silicon, or polymeric materials.<br>17. Patient has had a cerebrovascular accident or transient ischemic attack within 6 months prior to the study procedure . Except cases with an event associated with AS.<br>18. Patient with poorly controlled blood pressure.<br>19. Patient has serum albumin < 3.0 g/dL or body mass index (BMI) < 18.<br>20. Patient has uncontrollable diabetes mellitus.<br>21. Patient has active bacterial endocarditis or other active infection.<br>22. Patient has life expectancy < 12 months due to pre-operative non-cardiac comorbidity (e.g., cancer, chronic liver disease).<br>23. Patient is currently participating in an investigational drug or another device study. [Note: Trials requiring extended follow-up for products that were investigational, but have become commercially available, are not considered investigational trials].<br>24. Cardiovascular surgeons and cardiologists concluded that the patient is inappropriate for participating in this trial.<br><br><TF approach><br>25. Patient has significant tortuous aorta, diseases including abdominal aortic or thoracic aneurysm, or significant atheroma in the femoral artery or iliac artery that would prevent from proper placement of delivery system.<br>26. Patient has iliofemoral vessel characteristics that would preclude safe placement of 14F or 16F introducer sheath such as severe obstructive calcification and severe tortuosity, or minimum average vessel size less than 5.5 mm (6.0 mm for 16F introducer sheath). |
| Study Endpoints | **Primary Endpoint**<br>All-cause mortality at 1 year post-procedure (noninferiority verification) |



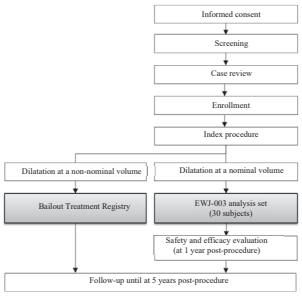


| Item | Content |
|---|---|
| | **Secondary Endpoints**<br><Secondary Safety Endpoints><br>• Composite endpoint: 30 days, 6 months, 1 year, and 2 to 5 years annually<br>○ Death and stroke<br>• Single endpoints: 30 days, 6 months, 1 year, and 2 to 5 years annually<br>○ Death (cardiovascular, non-cardiovascular)<br>○ MI (periprocedural, spontaneous)<br>○ Stroke (disabling, non-disabling)<br>○ Bleeding (life-threatening or disabling, major, minor)<br>○ Vascular access site/access-related complications<br>○ Major vascular complications<br>○ Conduction disturbance/arrhythmia<br>○ Conduction disturbance requiring new pacemaker implantation<br>○ Aortic valve re-intervention<br>○ Coronary obstruction<br>○ Endocarditis<br>○ Valve explants<br>○ Structural valve deterioration<br>○ Nonstructural valve dysfunction<br><br><Secondary Efficacy Endpoints><br>• Device success: 30 days<br>• Length of hospitalization /ICU stay: Discharge<br>• NYHA Classification: 30 days, 6 months, 1 year, and 2 to 5 years annually<br>• Six-minute walk test: 30 days and 1 year<br>• Quality of Life (QOL): 30 days, 6 months, 1 year, and 2 to 5 years annually<br><br><Secondary Valve Performance Endpoints><br>• Echocardiography: 30 days, 6 months, 1 year, and 2 to 5 years annually<br>○ Mean pressure gradient<br>○ Peak gradient<br>○ Effective orifice area (EOA)<br>○ Effective orifice area index (EOAi)<br>○ Aortic valve regurgitation (paravalvular, transvalvular)<br>○ Left Ventricular Ejection Fraction (LVEF) |

<table>
<tr><th>Item</th><th>Content</th></tr>
<tr><td></td><td>○ Left ventricular mass<br>○ Left ventricular mass index (LVMI)</td></tr>
<tr><td>Target Sample Size</td><td>A total of 30 subjects<br>• At least 2 subjects for each approach (TF, TA, and TAo) should be enrolled.<br>• At least 1 subject each for THV sizes.<br>• Enrollment will be closed when the number of patients enrolled in the study reaches the target sample size even when the above-mentioned number of patients are not ensured.<br>• Additional subjects will not be included for discontinued subjects.</td></tr>
<tr><td></td><td>
<table>
<tr><td>Target sample size by approach</td><td></td><td>Target sample size</td></tr>
<tr><td>Transfemoral</td><td>≥ 2 subjects</td><td rowspan="8">A total of 30 subjects</td></tr>
<tr><td>Transapical</td><td>≥ 2 subjects</td></tr>
<tr><td>Transaortic</td><td>≥ 2 subjects</td></tr>
<tr><td colspan="2">Target sample size by valve size</td></tr>
<tr><td>20 mm</td><td>≥ 1 subject</td></tr>
<tr><td>23 mm</td><td>≥ 1 subject</td></tr>
<tr><td>26 mm</td><td>≥ 1 subject</td></tr>
<tr><td>29 mm</td><td>≥ 1 subject</td></tr>
</table>
</td></tr>
<tr><td>Sample Size Calculation</td><td>The sample size for this trial was calculated based on the number of subjects required to verify noninferiority of the study treatment to the standard therapy by comparing the primary endpoint of all-cause mortality at 1 year post-procedure with the performance goal (PG). With the predicted mortality (true value) at 1 year post-procedure of 20% and PG of 45%, the number of subjects required to reject the null hypothesis ($H_0$: Mortality at 1 year post-procedure is ≥ 45%) with one-sided alpha of 0.05 was calculated as 24 subjects. A sample size of 24 subjects will provide 81.1% power by one-sided Fisher's exact test. To account for the drop-out, a total of 30 subjects was determined for the target sample size for this trial.</td></tr>
</table>





<table>
<tr><th>Item</th><th>Content</th></tr>
<tr><td>Bailout Treatment Registry</td><td>In this trial, a subject who received valve implantation with non-nominal balloon inflation volume as a result of the medical judgment will be considered "bailout subject" and registered to the Bailout Treatment Registry at the end of the study procedure . Bailout subjects will not be counted as the study target population (30 subjects), so that they will be excluded from the analysis population to evaluate the safety and effectiveness of EWJ-003. Post-procedure follow-up for them is the same as subjects with nominal valve implantation.<br> 
</td></tr>
<tr><td>Study sites</td><td>Maximum 3 sites in Japan</td></tr>
<tr><td>Study procedure</td><td><u>TF Approach</u><br>1. Using the crimper, crimp the THV on the valve crimping site of the delivery system after the THV rinsing.<br>2. Puncture the iliac-femoral artery by the standard procedure, and advance the guidewire to the left ventricle. Advance the balloon catheter from the femoro-iliac artery, and predilate the stenosed native aortic valve under the rapid pacing.<br>3. As maintaining guidewire position, remove the balloon catheter and subsequently expand the access site by using the introducer to place the introducer sheath.<br>4. Insert the delivery system through the sheath and advance it until descending aorta.<br>5. Initiate valve alignment by pulling the balloon shaft of delivery system, and transfer the THV on the balloon. Then advance the THV until the predilated native aortic valve.</td></tr>
</table>





<table>
<tr><th>Item</th><th>Content</th></tr>
<tr><td></td><td>6. Continuing the rapid pacing, dilate the balloon on the stenosed native aortic valve, and deploy the THV.<br><br><u>TA Approach</u><br>1. Using the crimper, crimp the THV on the balloon of the delivery system after the THV rinsing.<br>2. Access the apex through an anterior mini thoracotomy at the appropriate site. Incise the pericardium to expose the left ventricular apex.<br>3. Place a reinforced double purse string on the left ventricle apex, and insert the guidewire to the left ventricle through standard transapical techniques.<br>4. Advance the balloon catheter over the guidewire, predilate the stenosed native aortic valve under the rapid pacing.<br>5. Remove the balloon catheter, leaving the guidewire in place in the left ventricle. Subsequently, insert the introducer sheath over the guidewire and advance it to the left ventricular outflow tract (LVOT).<br>6. Insert the delivery system through the sheath and advance it until the predilated native aortic valve.<br>7. Continuing the rapid pacing, dilate the balloon on the stenosed native aortic valve, and deploy the THV.<br><br><u>TAo Approach</u><br>1. Using the crimper, crimp the THV on the balloon of the delivery system after the THV rinsing.<br>2. Access to the ascending aorta using standard surgical technique.<br>3. Place purse string sutures at the intended access site in the ascending aorta and insert the guidewire through standard transapical techniques.<br>4. Advance the balloon catheter over the guidewire, predilate the stenosed native aortic valve under the rapid pacing.<br>5. Remove the balloon catheter, leaving the guidewire in place in the left ventricle. Subsequently, insert the introducer sheath over the guidewire into the aorta to approximately 2 cm.<br>6. Insert the delivery system through the sheath and advance it until the predilated native aortic valve.<br>7. Continuing the rapid pacing, dilate the balloon on the stenosed native aortic valve, and deploy the THV.</td></tr>
<tr><td>Concomitant Medication/Procedur</td><td><u>Recommended Antiplatelet/Anticoagulation Regimen</u><br>< Pre-procedural antiplatelet therapy></td></tr>
</table>





<table>
<tr><th>Item</th><th>Content</th></tr>
<tr><td>e</td><td>Considering bleeding risk, pre-procedural antiplatelet is not applied as a general rule. If a patient was taking an antiplatelet or anticoagulant before procedure (excluding anticoagulant administration for dialysis), these medications should be discontinued at least 14 days prior to the study procedure .<br><br><Intraprocedural anticoagulation therapy><br>After intravenous administration of heparin 5000 IU, heparin will be given to achieve and maintain activated clotting time (ACT) ≥ 250 seconds.<br><br><Post-procedural antiplatelet therapy><br>Aspirin 75 to 100 mg/day will be given as a monotherapy for an indefinite period after study procedure .<br><br><u>Periprocedural dialysis</u><br><Pre-procedural dialysis><br>• For hemodialysis patients, perform hemodialysis until achievement of this dry weight on the day before study procedure as a general rule. Do not change the anticoagulant therapy.<br>• For peritoneal dialysis patients, continue peritoneal dialysis as usual until the day before study procedure .<br><br><Post-procedural dialysis><br>• Considering post-procedural hemodynamics, resume dialysis at the discretion of the investigator.<br>• In case of the hemodialysis, it is recommended to use anticoagulant with shorter half-life (e.g. nafamostat mesilate) to reduce bleeding risk.<br>• Do not change dialysis conditions until 1 year post-procedure as a general rule. However, the dialysis conditions may be changed if it is based on the medical judgement.</td></tr>
<tr><td>Follow-up Duration</td><td>For 5 years post-procedure</td></tr>
<tr><td>Schedule of Tests and Observations</td><td>As shown in Table I</td></tr>
<tr><td>Continued Access Registry</td><td>During a time period from the end of subject entry into the EWJ-003 analysis set until acquisition of marketing approval of the study device (EWJ-003), up to a maximum of 50 dialysis patients with severe AS requiring treatment with EWJ-003 will be included into the Continued Access Registry. Patients eligible for this registry must be verified that they meet all inclusion criteria for the</td></tr>
</table>

| Item | Content |
|---|---|
| | Continued Access Registry and do not fall under any of the exclusion criteria. The duration of post-procedural follow-up observation will be for 5 years post-procedure similarly to those for the EWJ-003 analysis set and bailout treatment registry, and tests/observations required for the Continued Access Registry will be performed. Subjects enrolled in this registry will not be included in the analysis set for the safety and efficacy evaluation of EWJ-003. |
| Inclusion Criteria for Continued Access Registry | 1. Patients determined by the heart team to be unable to undergo safe open surgical therapy and have the benefits of the study valve implantation. Specifically, considering the followings as risk factors, the risk should be comprehensively determined.<br>• Porcelain aorta<br>• History of mediastinal radiotherapy<br>• History of mediastinitis<br>• Remarkable thoracic deformity<br>• Previous open heart surgery or CABG<br>• Chronic obstructive pulmonary disease<br>2. Patient has senile degenerative AS with one of the following echocardiographic criteria. Measurement of AVA at baseline must be acquired within 60 days prior to the study procedure .<br>(a) Mean pressure gradient ≥ 40 mmHg<br>(b) Aortic flow velocity ≥ 4.0 m/s<br>(c) AVA at baseline ≤ 1.0 $cm^2$<br>(d) AVA index ≤ 0.6 $cm^2/m^2$<br>3. Patient has symptoms associated with AS ≥ NYHA class II.<br>4. The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the IRB of the respective clinical site.<br>5. The subject and the investigator agreed to comply with all required post-procedural follow-up visits.<br>6. Patient on maintenance dialysis (hemodialysis or peritoneal dialysis).<br>7. Patient has any one of the following native aortic valve annulus sizes as measured by TEE or 3D-CT.<br>(a) Native annulus size ≥ 16 mm and ≤ 28 mm by TEE<br>(b) Native annulus area ≥ 273 $mm^2$ and ≤ 683 $mm^2$ by 3D-CT<br>(c) Area-derived diameter ≥ 18.6 mm and ≤ 29.5 mm by 3D-CT |
| Exclusion Criteria for Continued Access | 1. Patient has an evidence of an acute MI within 1 month (30 days) prior to the study procedure . Acute MI is defined as; Q wave MI, or non-Q-wave MI |





| Item | Content |
|---|---|
| Registry | with elevation of CK-MB or troponin, together with the evidence of myocardial ischemia with at least one of the following findings:<br>• Symptoms of ischemia<br>• ECG changes indicative of new ischemia (ST-T changes, LBBB)<br>• Imaging evidence of a new loss of viable myocardium or new wall motion abnormality.<br>2. Patient has a congenital unicuspid or bicuspid aortic valve, or a non-calcified aortic valve.<br>3. Patient has severe aortic valve regurgitation.<br>4. Patient has severe mitral valve regurgitation.<br>5. Patient has an evidence of any therapeutic invasive cardiac procedures within 30 days prior to the study procedure . However, implantation of a permanent pacemaker or balloon valvuloplasty for bridging to procedure after a qualifying echocardiography are excluded.<br>6. Patient with planned concomitant surgical or transcatheter ablation for atrial fibrillation.<br>7. Patient has pre-existing prosthetic valve in any position.<br>8. Patient is at a high risk of bleeding, difficult to have appropriate treatment, or unable to receive appropriate anticoagulation or antiplatelet therapy.<br>• Leukopenia (white blood cell < 3,000 cells/$mm^3$)<br>• Thrombocytopenia (platelet < 50,000 cells/$mm^3$)<br>• Bleeding diathesis or coagulopathy<br>• Active gastro-intestinal ulceration, or upper gastro-intestinal bleeding within the past 3 months<br>• Refuse blood transfusion<br>• Receiving anticoagulant and/or antiplatelet medication unable to interrupt for the study procedure<br>• Concluded by investigator that appropriate anticoagulation or antiplatelet therapy is difficult for any other reasons<br>9. Patient has untreated clinically significant coronary artery disease requiring revascularization.<br>10. Patient has hemodynamic instability requiring mechanical heart assistance. Patient has respiratory instability requiring mechanical ventilation.<br>11. Patient requires an emergency surgery for any reason.<br>12. Patient has hypertrophic cardiomyopathy with or without obstruction.<br>13. Patient has severe ventricular dysfunction with LVEF < 20%.<br>14. Patient has echocardiographic evidence of intracardiac mass, thrombus, or |





| Item | Content |
|---|---|
| | vegetation.<br>15. Patient has hypersensitivity to or a known contraindication of heparin and/or aspirin, which cannot be adequately pre-medicated. Patient has a known hypersensitivity to contrast media.<br>16. Patient has hypersensitivities to cobalt, chromium, nickel, molybdenum, titanium, manganese, silicon, or polymeric materials.<br>17. Patient has had a cerebrovascular accident or transient ischemic attack within 6 months prior to the study procedure . Except cases with an event associated with AS.<br>18. Patient with poorly controlled blood pressure.<br>19. Patient has serum albumin < 2.8 g/dL or BMI < 16.<br>20. Patient has uncontrollable diabetes mellitus.<br>21. Patient has active bacterial endocarditis or other active infection.<br>22. Patient has life expectancy < 12 months due to pre-operative non-cardiac comorbidity (e.g., cancer, chronic liver disease).<br>23. Patient is currently participating in an investigational drug or another device study. [Note: Trials requiring extended follow-up for products that were investigational, but have become commercially available, are not considered investigational trials].<br>24. Cardiovascular surgeons and cardiologists concluded that the patient is inappropriate for participating in this trial.<br><br><TF approach><br>25. Patient has significant tortuous aorta, diseases including abdominal aortic or thoracic aneurysm, or significant atheroma in the femoral artery or iliac artery that would prevent from proper placement of delivery system.<br>26. Patient has iliofemoral vessel characteristics that would preclude safe placement of 14F or 16F introducer sheath such as severe obstructive calcification and severe tortuosity, or minimum average vessel size less than 5.5 mm (6.0 mm for 16F introducer sheath). |
| Schedule of Tests and Observations for Continued Access Registry | As shown in Table II |
| Study Duration | September 2016 to September 2025<br><br><EWJ-003 Analysis Population/Bailout Treatment Registry> [Enrollment closed] |





| Item | Content |
|---|---|
| | September 2016 to December 2022<br>The estimated period of subject enrollment into the EWJ-003 analysis population is from September 2016 to October 2017 (14 months). Clinical study report will be prepared after the completion of 1 year-data collection and utilized for the regulatory submission.<br><br>< Continued Access Registry ><br>January 2018 to September 2025<br>Subject entry into the Continued Access Registry will start from January 2018 to July 2020 (2 years and 6 months), after the completion of subject entry into the EWJ-003 analysis population. |

Table I: Schedule of Tests and Observations

| Tests/observations \ Timing | | Baseline (Within 60 days pre-procedure) | During procedure | Immediately after procedure (Within 72 hours pre-procedure) | Discharge or 7 days post-procedure (± 2 days) | 30 days post-procedure (- 7 days, + 14 days) | 6 months post-procedure (± 30 days) | 1 year post-procedure (± 30 days) | 2 - 5 years post-procedure (± 45 days) | Discontinued | Unscheduled visit |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed consent | | X | | | | | | | | | |
| Inclusion/exclusion criteria | | X | | | | | | | | | |
| Patient background | | X | | | | | | | | | |
| Surgical risk assessment*1 | | X | | | | | | | | | |
| NYHA classification of cardiac performance | | X | | | X | X | X | X | X | | |
| CCS status of stable angina | | X | | | X | X | X | X | X | | |
| Neurological assessment*2 (NIHSS, mRS) | | X | | | | X | X | X | | | |
| Blood pressure | | X | | | X | X | X | X | | | |
| 12-lead ECG | | X*3 | | X | X | X | X | X | | | |
| Chest X-ray | | X | | X | X | X | X | X | | | |
| Head CT | | X | | | | X | X | X | | | |
| 6-minute walk test | | X | | | | X | | X | | | |
| Clinical laboratory test | Hematology | X*4 | | | | X | X | X | | | |
| | Biochemistry | X*4 | | | | X | X | X | | | |
| | Coagulation | X*4 | | | | X | X | X | | | |
| | Cardiac enzyme | X*4 | | X | X | X | X | X | | | |
| Echocardiography | | X | X*8 | | X*11 | X*11 | X*11 | X*11 | X*11 | | |
| Cardiac CT | | X | | | | | | | | | |
| Coronary angiography | | X*5 | | | | | | | | | |
| Aortofemoral imaging | | X*6 | | | | | | | | | |
| Cardiac catheterization | | | X*9 | | | | | | | | |
| QOL questionnaire (EuroQOL, SF-12) | | X | | | | X | X | X | X | | |
| Procedure information | | | X | | | | | | | | |
| Anticoagulant/antiplatelet drugs | | X*7 | ← | | | | X | → | | | |
| Antibiotic | | X*7 | ← | X | → | | | | | | |
| Blood purification | | ← | X*10 | → | | | | X | | | |
| Other concomitant medication/therapy | | | ← | | X | → | | | | X*12 | X*12 |
| Adverse event/device deficiency | | | ← | | | | X | → | | | |

*1 Calculate STS score, Logistic EuroSCORE, and EuroSCORE II.
*2 For patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.
*3 Perform within 48 hours prior to entering the operating room.
*4 Perform within 14 days prior to the study procedure.
*5 Perform within 90 days prior to the study procedure.
*6 Perform CT, MRI, or X-ray within 90 days prior to the study procedure .
*7 Start assessment from 7 days pre-procedure.
*8 Measure the aortic annulus diameter, and perform observation items of cardiac catheterization according to the situation.
*9 Perform pre- and post-study procedure . May be performed by echocardiography according to the situation.
*10 Assess dialysis information performed from the latest date prior to the study procedure to discharge (at discharge date or 7 days post-procedure, whichever came earlier).
*11 Baseline BSA value must be used for calculation of EOAi and LVMI.
*12 Assess other concomitant medication/therapy used within 1 year post-procedure, excluding anticoagulation/antiplatelet, antibiotic, and hemodialysis.





Table II: Schedule of Tests and Observations for Continued Access Registry

| Tests/observations \ Timing | | Baseline (Within 60 days pre-procedure) | During procedure | Immediately after procedure (Within 72 hours pre-procedure) | Discharge or 7 days post-procedure (± 2 days) | 30 days post-procedure (- 7 days, + 14 days) | 6 months post-procedure (± 30 days) | 1 year post-procedure (± 30 days) | 2 - 5 years post-procedure (± 45 days) | Discontinued | Unscheduled visit |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed consent | | X | | | | | | | | | |
| Inclusion/exclusion criteria for Continued Access Registry | | X | | | | | | | | | |
| Patient background | | X | | | | | | | | | |
| Surgical risk assessment*1 | | X | | | | | | | | | |
| NYHA classification of cardiac performance | | X | | | X | X | X | X | X | | |
| CCS status of stable angina | | X | | | X | X | X | X | X | | |
| Neurological assessment*2 (NIHSS, mRS) | | X | | | | X | X*3 | X*3 | | | |
| Blood pressure | | X | | | X | X | X | X | | | |
| 12-lead ECG | | X*4 | | X | X | X | X | X | | | |
| Chest X-ray | | X | | X | X | X | X | X | | | |
| Head CT | | X | | | | X | X*3 | X*3 | | | |
| Clinical laboratory test | Hematology | X*5 | | | | X | X | X | | | |
| | Biochemistry | X*5 | | | | X | X | X | | | |
| | Coagulation | X*5 | | | | X | X | X | | | |
| | Cardiac enzyme | X*5 | | X | X | X | X | X | | | |
| Echocardiography | | X | X*9 | | X*12 | X*12 | X*12 | X*12 | X*12 | | |
| Cardiac CT | | X | | | | | | | | | |
| Coronary angiography | | X*6 | | | | | | | | | |
| Aortofemoral imaging | | X*7 | | | | | | | | | |
| Cardiac catheterization | | | X*10 | | | | | | | | |
| QOL questionnaire (EuroQOL, SF-12) | | X | | | | X*13 | X*13 | X*13 | X*13 | | |
| Procedure information | | | X | | | | | | | | |
| Anticoagulant/antiplatelet drugs | | X*8 | ← | | | | X | → | | | |
| Blood purification | | ← | X*11 | → | | | | X | | | |
| Other concomitant medication/therapy | | | ← | | X*14 | → | | | | X*14 | X*14 |
| Adverse event/device deficiency | | | ← | | | | X | → | | | |

*1 Calculate STS score, Logistic EuroSCORE, and EuroSCORE II.
*2 For patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.
*3 Subjects who developed stroke only.
*4 Perform within 48 hours prior to entering the operating room.
*5 Perform within 14 days prior to the study procedure.
*6 Except cases that may be clinically valid, perform within 1 year prior to the study procedure.
*7 Perform CT, MRI, or X-ray within 90 days prior to the study procedure.
*8 Start assessment from 7 days pre-procedure.
*9 Measure the aortic annulus diameter, and perform observation items of cardiac catheterization according to the situation.
*10 Perform pre- and post-study procedure . May be performed by echocardiography according to the situation.
*11 Assess dialysis information performed from the latest date prior to the study procedure to discharge (at discharge date or 7 days post-procedure, whichever came earlier).
*12 Baseline BSA value must be used for calculation of EOAi and LVMI.
*13 Subjects who were included in the continued access registry under Protocol ver. 5 will require no post-procedural QOL questionnaire.
*14 Where possible, assess other concomitant medication/therapy used within 1 year post-procedure, excluding anticoagulation/antiplatelet, antibiotic, and hemodialysis.





# 1 INTRODUCTION

## 1.1 Background of Development

### 1.1.1 Background of development of Transcatheter aortic valve implantation

Aortic stenosis (AS) is a disease condition in which constriction is developed in the aortic valve due to degeneration of the aortic valve, congenital bicuspid aortic valve, rheumatism, or inflammatory changes. In the recent aging population, the cause of AS has shifted from inflammatory changes due to rheumatic fever to degeneration by aging and arteriosclerosis, and the incidence in the elderly is predicted to be growing in the future. In degenerative AS progressive calcification of the cusp restricts normal cusp opening during systole. As a result, the left ventricle receives a chronic pressure load, leading to afferent left ventricular hypertrophy, reduced systemic and coronary blood flow. Typically, patients with AS are free from clinical symptoms, such as angina pectoris, syncope, or heart failure, for a long period of time in the course of the disease. However, once these symptoms manifest, the prognosis is poor; the mean life expectancy of 5 years after onset of angina pectoris, 3 years after syncope, and 2 years after heart failure.[1] Therefore, symptomatic and severe AS patients should receive surgery as soon as practicable.

The standard treatment for AS is surgical aortic valve replacement (sAVR) with which the hardened native cusp is removed under open-heart surgery and replaced with artificial valve. However, since sAVR requires extracorporeal circulation, and general anesthesia is essential, very old patients, patients with severe preoperative complication, and patients with significantly impaired cardiopulmonary function have a higher risk of periprocedural mortality and severe postoperative complication, and therefore sAVR is not applicable. Such patients receive drug therapies, including diuretics and vasodilator, only to alleviate the symptom. Other treatments for patients who cannot be treated with sAVR include percutaneous balloon aortic valvuloplasty that has been performed since around 1980. However, since many patients developed re-stenosis within 1 year after the procedure, percutaneous balloon aortic valvuloplasty is not presently performed as an active treatment means.

Under such circumstances, as a minimally invasive treatment for patients at a higher surgical risk and not eligible for sAVR, transcatheter aortic valve implantation (TAVI) has been developed in the recent years, with which a bioprosthetic valve is placed through a catheter. TAVI using balloon expandable device, which was clinically applied for the first time by Cribier, et al. in 2002,[2] followed by the 1st generation SAPIEN bioprosthetic valve system (hereinafter “SAPIEN”) gaining CE mark in EU in 2007, and in 2011 approved by the FDA in the US. Subsequently, the 2nd generation SAPIEN XT bioprosthetic valve system (hereinafter “SAPIEN XT”) was developed, with improved functions based on the findings obtained in the clinical use. SAPIEN XT gained CE mark in 2010, approved by the FDA in 2014, and in Japan sizes 23 mm and 26 mm were approved in 2013, and sizes 20 mm and 29 mm were approved by partial change application in 2015 (Approval No.: 22500BZX00270000). At present, in order to further minimize the risk of paravalvular regurgitation and vascular complication, the 3rd generation bioprosthetic valve system





(EWJ-003) with an additional back-flow prevention mechanism and reduced diameter has been developed, gaining CE mark in 2014, and approved by the FDA in 2015. Also in Japan, it was approved in March 2016 (Approval No.: 22800BZX00094000; transfemoral (TF) approach only), and expected to be widely usd in clinical practice in the near future.

### 1.1.2 AS treatment in chronic dialysis patients

In Japan, the number of chronic dialysis patients is growing every year, and according to the investigation by The Japanese Society for Dialysis Therapy,[3] the number reached 320,448 patients at the end of 2014. The annual crude death rate in 2014 was 9.6%, and as the cause of deaths, cardiovascular deaths, combining the largest number of heart failure (26.3%), cerebrovascular disorder (7.1%), and myocardial infarction (MI) (4.3%), accounted for 37.7%. AS is one of the major complications in dialysis patients, and compared with non-dialysis patients higher prevalence can be found in dialysis patients, with a reportedly higher complication prevalence rate of 3% to 15%.[4-8] In addition, it is known that since dialysis patients develop AS earlier,[9] and prone to develop ectopic calcification due to secondary hyperparathyroidism, AS is aggravated in about twice as faster than that in non-dialysis patients with progression of aortic valve calcification.[6, 10] Moreover, dialysis patients are susceptible to infective endocarditis associated with paracentesis at hemodialysis and their susceptibility to infection,[11] and often complicated with coronary artery disease.

Currently, of the treatments for AS in dialysis patients, the 1st line of treatment is sAVR. There is no difference in the indication of sAVR for AS between dialysis patients and non-dialysis patients, and in Japan it is based on “Guidelines for Surgical and Interventional Treatment of Valvular Heart Disease”[12] created by joint study group of 4 medical societies, including The Japanese Circulation Society, in 2012. However, compared with non-dialysis patients, dialysis patients have poor prognosis after sAVR.[13, 14] In addition, since early calcification of bioprosthetic valve and structural valve deterioration are concerned in dialysis patients because calcification is more likely to occur, for selection of prosthetic valve for dialysis patients, the use of mechanical valves has been typically recommended to date. However, since there is no difference in the long-term outcome results between dialysis and non-dialysis patients[15-17] and the incidence of valve-related complications is smaller with bioprosthetic valves, it was reported that bioprosthetic valves were favorable.[18, 19] Therefore, at present, it is recommended that valves be selected according to the patient’s condition, taking primary disease and complications into consideration.[12, 20]

Chronic dialysis patients have multiple complications in general, with poor general condition due to a bleeding tendency and increased susceptibility to infection, and have a higher surgical risk, and therefore compared with non-dialysis patients, dialysis patients are often not eligible for sAVR. As described above, TAVI may be considered in patients not eligible for sAVR; however in Japan the approved indication of SAPIEN XT and EWJ-003 is limited to non-dialysis patients with symptomatic severe AS associated with

sclerosis of the native aortic cusp, not eligible for surgery and deemed best treated with these devices, and hence chronic dialysis patients are not included. Because of this, chronic dialysis patients not subject to sAVR have no choice other than palliative symptomatic treatment with drug therapy at present, and inclusion of chronic dialysis patients into the indication of TAVI has been demanded.

### 1.1.3 TAVI development for chronic dialysis patients

To date, TAVI development for chronic dialysis patients in Japan has been initiated mainly by Osaka University Hospital. Osaka University Hospital performed TAVI using the 1st generation SAPIEN and 2nd generation SAPIEN XT in chronic dialysis patients with symptomatic severe AS, who were not eligible for sAVR under advanced medical care, and in 2015 Maeda et al. reported good results in 17 chronic dialysis patients up to 1 year after the procedure.[21] As of March 2016, the results in 24 chronic dialysis patients up to 1 year after the procedure have been obtained, and the treatment results are compared favorably with sAVR, the standard therapy. Therefore, TAVI could be a safe and effective treatment method in chronic dialysis AS patients who were not indicated for sAVR, and with no radical treatment available.

As described above, the safety and efficacy of TAVI using SAPIEN and SAPIEN XT in chronic dialysis patients in advanced medical care were evident. However, since newly introduced 3rd generation EWJ-003 has a paravalvular regurgitation preventing mechanism, with reduced diameter, it may serve as a safer and more effective treatment to chronic dialysis patients with multiple complications, bleeding tendency, and increased susceptibility to infection. In order to support the safety and efficacy of TAVI in chronic dialysis patients observed in advanced medical care, hypothesis should be tested in a statistically basis, and further by performing a long-term follow-up for 5 years after the procedure, long-term safety and efficacy need to be confirmed.

Based on the above, we planned this clinical trial to evaluate the safety and efficacy of TAVI using EWJ-003 in chronic dialysis patients.

## 1.2 Validity of the Trial Conduct

### 1.2.1 Nonclinical study results (For details see Investigator's Brochure)

Similarly to the already approved SAPIEN XT, the investigational valve is a device that combines a balloon expandable stent and bioprosthetic valve technology. Similarly to the existing device, to achieve an adequate hemodynamic improvement in AS patients, a moderate valve area should be ensured, and the shape should be maintained withstanding strong external load on the fibrous annular. Therefore, in order to evaluate the characteristics of the investigational device, nonclinical studies were conducted, considering not only valve performance but also functionality of the frame to fix the valve by expansion of a balloon. The studies conducted and specifications applied or referred to are presented in Table 1-1.





Table 1-1: Conducted nonclinical studies and specifications

| Studied item | Specifications applied or referred to |
|---|---|
| Risk management | ● ISO 14971: Application of risk management to medical devices<br>(ISO 14971 is the same as JIST 14971 "Medical devices - Application of risk management to medical devices.") |
| Physical and chemical property study | ● FDA Replacement Heart Valve Guidance Version 4.1 (dated October 14, 1994)<br>● ISO 5840: Cardiovascular implants - Artificial heart valve<br>● FDA Guidance for Intravascular Stents and Associated Delivery Systems (dated January 13, 2005)<br>● ISO 14630: Non-active surgical implants - General requirements<br>● ISO 25539-1: Cardiovascular implants - Intravascular devices - Part 1: Intravascular aids<br>● ISO 10555-1: Disposable sterile vascular catheter - Part 1: General requirements<br>● ISO 10555-4: Disposable sterile vascular catheter - Part 4: Balloon dilatation catheters<br>● ISO 11070: Disposable sterile vascular catheter inducer |
| Hydrodynamic study | ● FDA Replacement Heart Valve Guidance Version 4.1 (dated October 14, 1994)<br>● ISO 5840: Cardiovascular implants - Artificial heart valve |
| Accelerated durability study | ● FDA Replacement Heart Valve Guidance Version 4.1 (dated October 14, 1994)<br>● ISO 5840: Cardiovascular implants - Artificial heart valve |
| Biological safety study | ● ISO 10993-1: Biological evaluation of medical devices - Part 1: Evaluation and tests |
| Animal study | ● FDA 21 CFR part 58 GLP<br>● ISO 5840: Cardiovascular implants - Artificial heart valve |

The investigational valve and delivery system were individually tested with application or in reference to the specifications shown in the above table, and the results confirmed the performance and safety of the investigational valve.





### 1.2.2 Clinical trial results (For details see Investigator's Brochure)

#### 1.2.2.1 Clinical trial results of the investigational device

Clinical trials of this investigational device are listed in Table 1-2.

Table 1-2: List of clinical trials of this investigational device

| | Study title | Study objective | Study design | Country/ region | Study device (size) | Implantation procedure | Target sample size | Number of study sites | Study progression status |
|---|---|---|---|---|---|---|---|---|---|
| 1 | First-in-man trial | Feasibility study | Prospective, multi-center study | Canada | EWJ-003 (26) | TF | 15 subjects | 2 sites | Completed |
| 2 | PARTNER II Trial (2010-12-US) | To evaluate the safety and efficacy of a bioprosthetic valve and delivery system | A prospective, single arm, non-randomized, historical control comparative study | US | EWJ-003 (20, 23, 26, 29) | TF, TA, TAo | 583 subjects* (TF: 491 subjects) | 29 sites | Follow-up observation is underway |
| 3 | EU clinical trial (2012-07) | To evaluate the safety and efficacy of a bioprosthetic valve and delivery system | Prospective, non-randomized, multi-center study | EU, Canada | EWJ-003 (20, 23, 26, 29) | TF, TA, TAo | 102 subjects* (TF: 57 subjects) | 14 sites | Follow-up observation is underway |

* The number of subjects valid for analysis of results in patients not eligible for surgery and at a higher risk used for approval application of EWJ-003 in Japan.

**<First-in-man trial>**

A first-in-man trial of EWJ-003 was conducted in Canada[22] from January to June 2012, 15 patients with symptomatic severe AS (including 1 chronic dialysis patient) were enrolled in this clinical trial from 2 trial sites. The average patient age was 80.3 ± 11.2 years, and male patients accounted for 100%, with the Society of Thoracic Surgeons (STS) score of 5.4 ± 3.2%. All patients received the procedure by TF approach, and the investigational valve was successfully implanted. There were no death cases within 30 days post-procedure, and no incidence of stroke, vascular complications, or bleeding was observed. No cases with moderate to severe paravalvular regurgitation within 30 days post-procedure were reported, and all subjects were assessed as New York Heart Association (NYHA) Class I or Class II. Also the effective orifice area (EOA) and mean pressure gradient determined by echocardiography were significantly improved from the baseline at 30 days after the procedure, and post-procedural good hemodynamics was confirmed.

**<PARTNER II Trial>**

PARTNER II Trial conducted in the US evaluated the safety and efficacy of EWJ-003 in severe AS patients with symptomatic calcification (excluding chronic dialysis patients). From October 2013 to July 2014, 586 subjects who were not eligible for surgery and at a higher risk were enrolled from 29 study sites, of which 583 subjects received investigational valve implantation. The implantation procedures included TF approach in 491 subjects, transapical (TA) approach in 57 subjects, and transaortic (TAo) approach in 35





subjects. For this trial, a long-term follow-up is still underway, and at this time point, the results up to 1 year after the procedure have been obtained.

The average patient age of these 583 subjects who received implantation of the investigational valve was 82.6 ± 8.1 years, and a proportion of male patients was 58.0%, with the mean STS score and Euro SCORE II of 8.6 ± 3.7% and 8.6 ± 7.1%, respectively. Of 583 subjects, 581 subjects (99.7%) received the investigational valve implantation as assigned, and only 1 subject was switched to surgery. The remaining 1 subject was transferred from TF approach to TA approach due to an intraoperative complication. The incidence of nonhierarchical composite events consisting of the primary endpoints; all-cause mortality, all stroke, and ≥ moderate aortic valve regurgitation, at 30 days after the procedure, was 6.7% in the EWJ-003 group and 15.6% in the historical control SAPIEN group. The difference was -9.0% (90% confidence interval [CI]: -13.1%, -5.2%). Since the upper limit of the 90% CI of -5.2 was lower than the noninferiority margin of 7.5%, the noninferiority of EWJ-003 to SAPIEN was verified. All incidence of ≥ moderate aortic valve regurgitation and severe vascular complications at 30 days post-procedure were significantly lower with EWJ-003 compared with SAPIEN, and thus the concept of EWJ-003 development was achieved [Aortic valve regurgitation: SAPIEN group, 14.3%; EWJ-003 group, 3.0%, $p < 0.0001$, severe vascular complication: SAPIEN group, 10.1%; EWJ-003 group, 5.0%, $p = 0.0006$]. The incidence determined by the Kaplan-Meier estimates for all-cause mortality and stroke at 30 days post-procedure were 2.2% and 1.4%, respectively, and at 1 year post-procedure 14.4% and 4.3%, respectively. At 30 days post-procedure 87.3% of subjects showed improvement of ≥ NYHA Class I, and also at 1 year post-procedure sustained improvement was observed. Also long-term outcome of hemodynamics was good, the EOA, mean pressure gradient, and maximum pressure gradient determined by echocardiography were significantly improved from the baseline at 30 days after the procedure, and at 1 year post-procedure sustained improvement was observed.

**[By approach]**

**<u>TF Approach</u>**

The background of 491 subjects who received the procedure via TF approach was comparable to that of the overall subject population; the average patient age of 82.8 ± 8.2 years, and a proportion of male patients was 56.4%, with the mean STS score and Euro SCORE II of 8.4 ± 3.5% and 8.2 ± 6.8%, respectively. Of 491 subjects, 78 subjects (15.9%) received the procedure with conscious sedation method, and the average duration of procedure was shorter with TF approach, compared with TA/TAo approaches. The investigational valve was implanted at the intended position in 99.4% of subjects, and postprocedural dilatation was required in 14.9% of subjects. The length of postprocedural hospitalization was 6.1 ± 4.3 days, which was shorter than that of TA/TAo approaches. Late clinical outcome showed the same trend as that of overall subjects. The incidence determined by the Kaplan-Meier estimates for all-cause mortality and stroke at 30 days post-procedure were 1.6% and 1.4%, respectively, and at 1 year post-procedure 12.3% and 4.1%, respectively, which were lower than those of TA/TAo approaches. On the other hand,

vascular access site/access-related complications that are concerned with TF approach were common compared to those of TA/TAo approaches, but the incidence of severe vascular complications was equivalent.

**TA Approach**

The average age of 57 subjects who received the procedure via TA approach was 80.0 ± 7.2 years, which was comparable to that of overall subjects. On the other hand, the male ratio (77.2%) was higher than that of overall subjects, and the STS score and EuroSCORE II were also higher as 9.3 ± 3.9% and 11.3 ± 8.4%, respectively. All subjects received the procedure with general anesthesia, and the average duration of procedure was longer than that of TF approach but shorter than that of TAo approach. The investigational valve was implanted at the intended position in 96.5% of subjects, and postprocedural dilatation was required in 14.0% of subjects. The length of postprocedural hospitalization was 9.8 ± 6.2 days, which was longer than that of TF approach. As for late clinical outcome, compared with TF approach, its prognosis was poorer; the incidence determined by the Kaplan-Meier estimates for all-cause mortality at 30 days post-procedure and 1 year post-procedure were 3.5% and 22.8%, respectively. The incidence of stroke at 30 days post-procedure was 1.8%, and at 1 year post-procedure 8.4%. Hemorrhage had been reported in 38.6% of subjects at 30 days post-procedure, which was higher than that with TF approach, but the incidence of life-threatening or disabling bleeding event was 5.3%, which was equivalent to that with TF approach.

**TAo Approach**

The average age of 35 subjects who received the procedure via TAo approach was 84.5 ± 7.1 years, which was comparable to that of overall subjects. On the other hand, a proportion of male subjects (48.6%) was lower than that of overall subjects, and the STS score and EuroSCORE II were higher as 11.1 ± 4.7% and 9.8 ± 7.7%, respectively. All subjects received the procedure with general anesthesia, and the longest average duration of procedure was observed with TAo approach, compared with other approaches. The investigational valve was implanted at the intended position in all subjects, and postprocedural dilatation was required in 14.3% of subjects. The length of postprocedural hospitalization was 11.4 ± 3.7 days, which was the longest duration, while the length of intensive care unit (ICU) stay was comparable to that with TA approach. As for late clinical outcome, compared with other approaches, its prognosis was poorer; the incidence determined by the Kaplan-Meier estimates for all-cause mortality at 30 days post-procedure and 1 year post-procedure were 8.6% and 29.2%, respectively. TAo approach resulted in a higher incidence of hemorrhage, which was reported in 51.4% of subjects at 30 days post-procedure, and 17.1% was assessed as life-threatening or disabling hemorrhage. On the other hand, no stroke had been reported at 1 year post-procedure.

**<EU clinical trial>**

EU clinical trial conducted in Europe and Canada evaluated the safety and efficacy of EWJ-003 in severe





AS patients with symptomatic calcification (excluding chronic dialysis patients). In this trial, 50 patients who were not eligible for surgery and at a higher risk were sequentially enrolled first, followed by enrollment of 100 patients ≥ moderate surgery risk. At this timepoint, the results up to 1 year after the procedure analyzing 102 subjects not eligible for surgery and at a higher risk who completed the follow-up observations at 1 year post-procedure as of September 4, 2014 are available. From January to October 2013, 102 subjects valid for analysis were enrolled in this clinical trial from 14 study sites, and all subjects received implantation of the investigational valve. The implantation procedures included TF approach in 57 subjects, and TA approach or TAo approach in 45 subjects.

The average age of these 102 subjects valid for analysis was 84.1 ± 5.0 years, and a ratio of male patients was 39.2%, with the mean STS score and Euro SCORE II of 8.0 ± 4.7% and 24.1 ± 13.0%, respectively. Of 102 subjects, 101 subjects (99.0%) received implantation of the investigational valve with no problem, and the procedure was switched to surgery in only 1 subject. The incidence of nonhierarchical composite events consisting of the primary endpoints; all-cause mortality, all stroke, and ≥ moderate aortic valve regurgitation, was 14.8% at 30 days after the procedure and 30.5% at 1 year post-procedure. The proportion of subjects with ≥ moderate aortic valve regurgitation was 9.8% at baseline, whereas it significantly decreased to 3.7% at 30 days, and 1.6% at 1 year post-procedure. Also the incidence of severe vascular complications was low; the rate at 30 days post-procedure was 4.9%. The incidence determined by the Kaplan-Meier estimates for all-cause mortality and stroke at 30 days post-procedure were 7.8% and 3.0%, respectively, and at 1 year post-procedure 19.9% and 5.4%, respectively. At 30 days post-procedure 92.1% of subjects showed improvement of ≥ NYHA Class I, and also at 1 year post-procedure sustained improvement was observed. Also long-term outcome of hemodynamics was good, the EOA, mean pressure gradient, and maximum pressure gradient determined by echocardiography were significantly improved from the baseline at 30 days after the procedure, and at 1 year post-procedure sustained improvement was observed.





**[By approach]**

**TF Approach**

The background of 57 subjects who received the procedure via TF approach was comparable to that of the overall subject population; the average patient age of 85.1 ± 4.6 years, and a proportion of male patients was 40.4%, with the mean STS score and mean Logistic EuroSCORE of 8.2 ± 4.2% and 22.3 ± 11.3%, respectively. Of 57 subjects, 13 subjects (22.8%) received the procedure with conscious sedation method, and the average duration of procedure was slightly longer, compared with TA/TAo approaches, as 86.1 ± 88.1 minutes, this may be because affected by that the procedure was switched to surgery in 1 subject. The investigational valve was implanted at the intended position in 98.2% of subjects, and postprocedural dilatation was required in 5.3% of subjects. The length of postprocedural hospitalization was 12.0 ± 7.8 days, which was shorter than that of TA/TAo approaches. Late clinical outcome showed the same trend as that of overall subjects. The incidence determined by the Kaplan-Meier estimates for all-cause mortality and stroke at 30 days post-procedure were 3.5% and 1.8%, respectively, and at 1 year post-procedure 12.4% and 3.6%, respectively, which were lower than those of TA/TAo approaches. Also for the vascular access site/access-related complications that are generally concerned with TF approach, a lower incidence was observed than those of TA/TAo approaches as 7.1%.

**TA/TAo Approaches**

The background of 45 subjects who received the procedure via TA/TAo approaches was comparable to that of the overall subject population; the average age of 83.0 ± 5.3 years, and a proportion of male patients was 37.8%, with the mean STS score and mean Logistic EuroSCORE of 7.9 ± 5.2% and 26.4 ± 14.7%, respectively. All subjects received the procedure with general anesthesia, and the average duration of procedure was 84.4 ± 28.8 minutes. The investigational valve was implanted at the intended position in all subjects, and postprocedural dilatation was required in 2.2% of subjects. The length of postprocedural hospitalization was 17.6 ± 11.3 days, which was longer than that of TF approach. As for late clinical outcome, compared with TF approach, the prognosis was poorer. The incidence determined by Kaplan-Meier estimates for all-cause mortality and stroke at 30 days post-procedure were 13.3% and 4.6%, respectively, and at 1 year post-procedure 29.2% and 7.9%, respectively. Hemorrhage had been reported in 35.8% of subjects at 30 days post-procedure, which was higher than that with TF approach, but the incidence of life-threatening or disabling bleeding event was 6.7%, which was equivalent to that with TF approach.

### 1.2.2.2 Treatment results in advanced medical care

Osaka University Hospital performed TAVI using the 1st generation SAPIEN and 2nd generation SAPIEN XT in chronic dialysis patients with symptomatic severe AS, who were not eligible for sAVR under advanced medical care. At present, the results in 24 Japanese chronic dialysis patients up to 1 year after the procedure have been obtained.





The mean age of 24 chronic dialysis patients who received TAVI was 76.7 ± 5.1 years, significantly lower than non-dialysis patients, and the proportion of male was 41.7%. The STS score was 15.0 ± 10.7%, and Logistic EuroSCORE was 27.3 ± 17.8%; compared with non-dialysis patients, surgical risk was higher. The average dialysis period was 11.8 ± 9.3 years. Of 24 subjects, 10 subjects received the procedure by TF approach, 14 subjects received TA approach, and the median length of postprocedural hospitalization and ICU stay were 13.8 days and 3.0 days, respectively. There were no death cases within 30 days post-procedure, and stroke was reported in 1 subject (4.1%). The survival rate at 1 year post-procedure determined by Kaplan-Meier survival analysis was as good as 89.3%, and also the event-free rate of major adverse cardiovascular and cerebral events (MACCE) at 1 year post-procedure of 71.4% was favorable in comparison with the event-free rate (60.5%) at sAVR in dialysis patients reported by Umezu et al. .[23] Also long-term outcome of hemodynamics was good, the effective orifice area index (EOAi) and mean pressure gradient, significantly improved from the baseline at 30 days post-procedure, and also at 1 year post-procedure sustained improvement was observed.

### 1.2.2.3 Referenced literature reports

It has been reported that the early and long-term mortality risk after TAVI increase depending on the severity of chronic kidney disease (CKD).[24 - 27] According to the report by Dumonteil et al.,[24] the mortality within 30 days post-procedure was 1.8% in non-CKD patients, whereas it was 6.7%, 8.3%, and 8.3% in mild, moderate, and severe CKD patients, respectively, and it was as high as 15.2% in dialysis patients. Also Allende et al.[25] classified 2075 patients undergone TAVI into 5 groups by the severity of CKD, and reported that higher early and medium-term mortality was found in severe CKD patients (Stage 4: eGFR ≥ 15 mL/min/1.73 $m^2$ and < 30 mL/min/1.73 $m^2$, and Stage 5: eGFR < 15 mL/min/1.73 $m^2$ or requiring dialysis), and the death-free rate at 1 year post-procedure was significantly lower in Stage 5 patients (64.5%). Moreover, recently conducted 2 European large-scale registry studies; FRANCE-2 registry[26] and UK TAVI registry[27], also examined the impact of CKD on TAVI treatment results, and reported that poor prognosis after TAVI was observed with advance in CKD. The mortality rate in the Stage 5 patient group including dialysis patients at 1 year post-procedure in FRANCE-2 registry[26] was 39.9% (of 96 Stage 5 patients, 82 patients were requiring dialysis), and in UK TAVI registry[27] it was 39.4% (of 99 Stage 5 patients, 81 patients were requiring dialysis). On the other hand, Rau et al.[28] reported that there was no difference in the Kaplan-Meier estimate mortality at 6 months after the procedure between 116 non-dialysis patients and 10 dialysis patients, who received TAVI due to ineligibility for surgery. Kobrin et al.[29] adjusted propensity score, and then compared the results between TAVI and sAVR in chronic dialysis patients. The mortality at 30 days post-procedure was 10% for TAVI and 8% for sAVR, with no statistically significant difference between these 2 treatment groups ($p$ = 0.47). Also for the survival rate at 1 year post-procedure determined by Kaplan-Meier survival analysis, no difference was found between 2 groups; 60% for TAVI and 63.6% for sAVR (Logrank $p$ = 0.99). According to the study by Alqahtani et al. in

2017[30], the hospital mortality adjusted for propensity score was 6.1% for TAVI and 13.7% for sAVR, with a significantly lower rate for TAVI ($p$ = 0.021). The hospital mortality by approach was 5.1% for TF approach (vs. 13.8% for sAVR, $p$ = 0.007) and 10% for TA approach (vs. 14% for sAVR 14%, $p$ = 0.52). Based on these reports, it is predicted that TAVI in chronic dialysis patients may lead to poorer prognosis compared with that in non-dialysis patients, but has the comparable safety and efficacy to those of sAVR, the standard treatment.

### 1.2.3 Validity of the trial conduct

Based on the fact that the quality, performance, and safety of this study device EWJ-003 were verified by non-clinical studies, a first-in-man trial of EWJ-003 was conducted in Canada. The first-in-man trial exploratory evaluated feasibility of EWJ-003 implantation by TF approach, and confirmed the basic safety and efficacy of EWJ-003. Subsequently, PARTNER II Trial conducted as a US IDE pivotal study and an EU clinical trial aiming at acquisition of CE mark showed the safety and efficacy of EWJ-003, and CE mark was granted in 2014, followed by FDA approval in 2015. Also in Japan, the TF approach was approved in March 2016 (Approval No.: 22800BZX00094000), and therefore it will be widely used in clinical practice in the near future. For the safety and efficacy of TAVI in Japanese chronic dialysis patients, advanced medical care performing TAVI with the 1st generation SAPIEN and 2nd generation SAPIEN XT confirmed the safety and efficacy up to 1 year after the procedure. In addition, since the study device EWJ-003 has a paravalvular regurgitation preventing mechanism, with reduced diameter of the system, this clinical trial of EWJ-003 is expected to show the results equal to or better than the results of advanced medical treatments using previous generation of the study device. Furthermore, chronic dialysis patients outside Japan are not excluded from the indications of TAVI devices including EWJ-003, and in view of the literature data on TAVI in chronic dialysis patients that have been reported outside Japan to date, it is predicted that TAVI in chronic dialysis patients may lead to poorer prognosis compared with that in non-dialysis patients, but has the comparable safety and efficacy to those of sAVR, the standard treatment.

Based on the above, it was determined that the conduct of this clinical trial for the purpose of evaluation of the safety and efficacy of EWJ-003 in chronic dialysis patients with symptomatic severe AS associated with sclerosis of the native cups of aortic valve is scientifically and ethically reasonable.

## 2 STUDY OBJECTIVE

The objective of this trial is to evaluate the safety and efficacy of EWJ-003 in chronic dialysis patients with symptomatic severe AS associated with sclerosis of the native cusp of aortic valve, who are deemed not to tolerate open surgery, and judged EWJ-003 is the best available treatment.





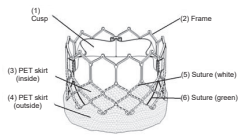
## 3 OUTLINE OF STUDY DEVICE

This clinical trial will use EWJ-003, the 3rd generation balloon expandable transcatheter bovine pericardial tissue valve developed by Edwards Lifesciences, as the study device. EWJ-003 is comprised of the transcatheter heart valve (THV), delivery system (for TF approach or TA/TAo approaches), and other components (crimper, crimping accessories, and inflation device/inflation syringe). The sizes of THV available in the trial are 20, 23, 26, and 29 mm.

| Native valve annulus size (TEE) | Native valve annulus size (CT) | | THV size | Valve height |
|---|---|---|---|---|
| | Area | Area derived diameter | | |
| 16 - 19 mm | 273 - 345 $mm^2$ | 18.6 - 21.0 mm | 20 mm | 15.5 mm |
| 18 - 22 mm | 338 - 430 $mm^2$ | 20.7 - 23.4 mm | 23 mm | 18 mm |
| 21 - 25 mm | 430 - 546 $mm^2$ | 23.4 - 26.4 mm | 26 mm | 20 mm |
| 24 - 28 mm | 540 - 683 $mm^2$ | 26.2 - 29.5 mm | 29 mm | 22.5 mm |

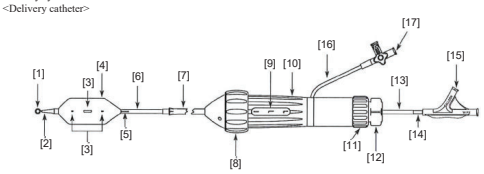
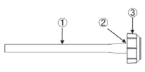
Table 3-1: THV sizes available in the trial

### 3.1 Structure or Composition of Study Device

| | Components | Outline |
|---|---|---|
| Investigational valve (common to TF, TA/TAo approaches) | | |
| 1 | THV   | The investigational valve (THV) is a device that combines a balloon expandable stent and bioprosthetic valve technology. Four valve sizes (20 mm, 23 mm, 26 mm, and 29 mm) are available, and designed for implantation by TF approach or TA/TAo approaches in severe AS patients. THV is comprised of a cusp (1) and a radiopaque, cobalt-chromium supporting structure (frame) to maintain the valve structure (2), and the frame is equipped with inner and outer polyethylene terephthalate (PET) fabric skirts (3,4) to prevent paravalvular regurgitation. These PET skirts are sewn on the frame by suture (5). The valve tissue is fabricated from bovine pericardium that have been preserved in low concentration solutions of buffered glutaraldehyde to fully crosslink the tissue, while preserving its flexibility and strength, molded into three equal cusps. |

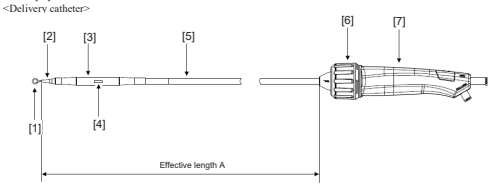
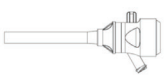


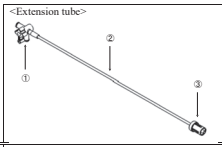
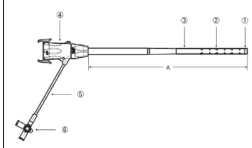
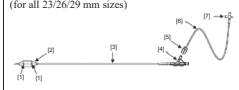


| | | |
|---|---|---|
| Delivery system (TF approach) | | |
| 1 | Delivery system<br><Delivery catheter>   | |
| | 1 Stylet<br>2 Tapered tip<br>3 Marker band<br>4 Balloon<br>5 Marker band<br>6 Crimp balloon<br>7 Flex catheter<br>8 Flex wheel<br>9 Flex indicator<br>10 Handle<br>11 Fine adjustment wheel<br>12 Balloon lock<br>13 Balloon catheter<br>14 Strain relief<br>15 Y-connector<br>16 Extension tube<br>17 Three-way stopcock | The delivery catheter is used to aid in insertion of the THV from the sheath along the guidewire into the body and allow to pass the aortic arch. The flex wheel enables the distal end of the catheter to curve, and the flex indicator allows us to know the angle at the curving. The tapered tip of the catheter facilitates easier passing through the native valve, and the balloon is used to deploy the THV. The THV is attached to the crimp site, and guided to the accurate site by the fine adjustment wheel. |
| 2 | Introducer sheath set<br><Sheath (expandable)>  <br><Introducer>  <br><Loader>   | An introducer sheath set is comprised of a sheath, an introducer, and a loader. A radiopaque marker in the distal end of the sheath is provided to visualize the position of the tip of sheath under X-ray fluoroscopy. The loader is used to insert the crimped THV mounted on the delivery system through the sheath. |



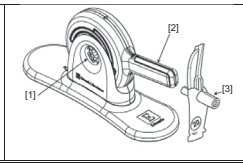


| | | |
|---|---|---|
| 3 | Balloon catheter  | The balloon catheter is utilized for balloon predilatation to help with THV delivery through the native valve. A radiopaque marker in the balloon is provided to visualize the position under X-ray fluoroscopy. |
| Delivery system (TA/TAo approach) | | |
| 1 | Delivery system<br><Delivery catheter>   | |
| | 1 Stylet<br>2 Tapered tip<br>3 Balloon<br>4 Marker band<br>5 Balloon catheter<br>6 Catheter knob<br>7 Handle | The delivery system is comprised of a delivery catheter, a loader, and an extension tube. The balloon has 2 radiopaque markers, which play a role of indicator not only in visualizing the balloon but also in visualizing the position of the THV during crimping. The catheter is equipped with a curving mechanism for positioning of the balloon. The loader is one of delivery system's components, and is intended to pass the valve mounted on the delivery catheter through a hemostasis valve located on the sheath introducer. |
| | <Loader>  | |

| | | |
|---|---|---|
| | <Extension tube><br>  | |
| 2 | Introducer sheath set<br><Sheath><br>  | The introducer sheath set is comprised of a sheath and an introducer. A radiopaque marker in the distal end of the sheath is provided to visualize the position of the tip of sheath under X-ray fluoroscopy. |
| | <Introducer><br>  | |
| 3 | Balloon catheter<br>(for all 23/26/29 mm sizes)<br>  | The balloon catheter is utilized for balloon predilatation to help with THV delivery through the native valve. A radiopaque marker in the balloon is provided to visualize the position under X-ray fluoroscopy.<br>The balloon catheter (20 mm) for the size 20 mm THV is the same product as the balloon catheter for 20 mm THV in the TF system. |
| | (20 mm)<br>  | |
| Other components (common to TF and TA/TAo approaches) | | |
| 1 | Crimper | The crimper is a device for single use that does not come into contact with the patient, which reduces the diameter of the THV symmetrically from expanded size to attaching size to mount it to the delivery balloon catheter. The crimper is comprised of a compression mechanism |

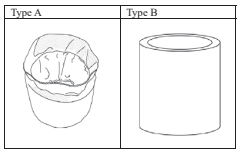
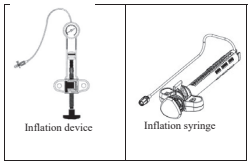




| | | |
|---|---|---|
| |  <br> | that is closed with a handle located on the housing.<br>The crimper includes a crimp stopper (packaged with the delivery system) to correctly crimp the THV to the appropriate size. |





| | | |
|---|---|---|
| 2 | Crimping accessories<br>  <br> | The crimping accessories (packaged with the delivery system) are utilized to protect the cusps during compression of the THV. Type A that corresponds with the size of the THV and Type B that is independent from the size are available. |
| 3 | Inflation device/inflation syringe<br>  <br> | The inflation device (20, 23, and 26 mm) and inflation syringe (29 mm only) are utilized to expansion/deflation of the balloon for predilatation and deployment of the THV. |

### 3.2 Directions for Use

Deliver a transcatheter heart valve (THV), the investigational valve, from the femoral artery, apex, or aorta to a lesion where the valve is deployed and implanted. The balloon inflation volume at deployment of THV is as shown in Table 3-2. For further descriptions of the study device see Attachment 2 "Instructions for Use."

Table 3-2: Balloon inflation volume required for deployment of THV

| Delivery system | | THV | Nominal volume |
|---|---|---|---|
| Transfemoral Approach | Model 9610TF20 | 20 mm | 11 mL |
| | Model 9610TF23 | 23 mm | 17 mL |
| | Model 9610TF26 | 26 mm | 23 mL |
| | Model 9610TF29 | 29 mm | 33 mL |
| Transapical/Transaortic Approaches | Model 9620TA20 | 20 mm | 14 mL |
| | Model 9620TA23 | 23 mm | 17 mL |
| | Model 9620TA26 | 26 mm | 23 mL |
| | Model 9620TA29 | 29 mm | 30 mL |





## 4 STUDY DESIGN

### 4.1 Study Design

This clinical trial is a prospective, open, non-randomized, multi-center, single arm study.

This trial evaluate the safety and efficacy of EWJ-003 in patients who were deemed medically inappropriate for sAVR and EWJ-003 therapy would be the best treatment available by the heart team, among chronic dialysis patients with symptomatic severe AS. Since the standard therapy of chronic dialysis patients with symptomatic severe AS is sAVR, the performance goal (PG) will be set based on the clinical research results of sAVR in chronic analysis patients, and non-inferiority of this clinical trial results of EWJ-003 to the standard therapy will be verified.

In this clinical trial, patients in whom deployment of the THV by balloon dilatation at a nominal volume was impossible for a medical reason during study procedure will be regarded as bailout cases, and these cases will be included in the bailout treatment registry at the end of the study procedure. The bailout cases will be enrolled separately from the target sample size of this trial, and will not be included in the analysis set for the safety and efficacy evaluation of EWJ-003.

In this clinical trial, on humanitarian grounds, subject enrollment will be continued as an continued access until EWJ-003 gains marketing approval, so that the subjects will be able to receive EWJ-003 therapy continuously even after completion of subject entry into the EWJ-003 analysis set. For the continued access registry, see Section 4.4.

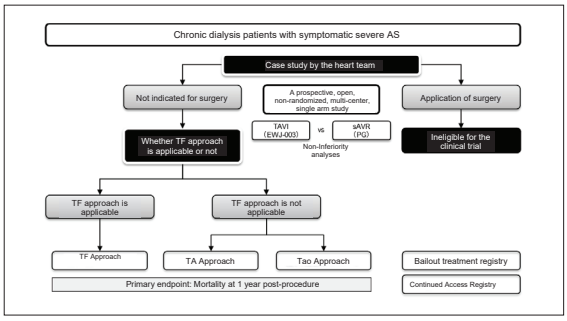



Figure 4-1: Study design of this clinical trial

<Rationales for the setting>

The standard therapy for chronic dialysis patients with symptomatic severe AS is sAVR. Therefore chronic dialysis patients deemed medically inappropriate for sAVR have no choice other than palliative symptomatic treatment with drug therapy at present. Based on that the clinical positioning of the treatment with EWJ-003 where EWJ-003 therapy may make curative therapy not inferior to the standard therapy sAVR possible in such chronic dialysis patients who were deemed medically inappropriate for sAVR, this clinical trial was designed to verify non-inferiority of EWJ-003 therapy to sAVR. The patients subject to EWJ-003 therapy are chronic dialysis patients at a higher surgical risk and cannot tolerate sAVR, and compared with patients undergoing sAVR, they have poorer general condition and therefore poor prognosis can be predicted. However, according to the report by Kobrin et al.[29] who adjusted patient background by propensity score adjustment method and compare the results of TAVI in chronic dialysis patients and the results of sAVR, but no statistically significant difference was found in these results, and therefore it was determined that for verification of non-inferiority of EWJ-003 therapy to sAVR, the difference may be clinically permissible.

Furthermore, since this clinical trial will be conducted in chronic dialysis patients who cannot receive sAVR, setting a control group of patients undergoing sAVR for randomized comparison is ethically not possible. Therefore, this clinical trial is designed as a single arm of EWJ-003 therapy, and for a control sAVR treatment results, PG will be set based on the results of Japanese clinical research reports.

## 4.2 Performance Goal

### 4.2.1 Rationales for the performance goal setting

The PG was established by estimating mortality at 1 year post-procedure from the clinical research results of sAVR in chronic dialysis patients in Japan.

In the dialysis treatment between Japan and Europe and the US, there are some differences in physique of the patients, formulation of dialysis volume and duration of dialysis, patient control, and treatment compliance, and it is generally known that prognosis is better in Japan relative to Europe and the US. According to a large-scale global observation epidemiologic cohort research on medical care process and outcome of patients on maintenance dialysis (Dialysis Outcomes and Practice Patterns Study [DOPPS]), when the relative death risk adjusted for age, gender, race, and 15 concomitant diseases in Japan is assumed to be 1, it was 3.78 in the US, and 2.84 in Europe[31]. Compared with non-dialysis patients, chronic dialysis patients have poorer prognosis after sAVR; it has been reported that the survival rate at 1 year post-procedure in the US was approximately 60%, at 3 years post-procedure approximately 40%, and at 5 years post-procedure approximately 30%,[9, 13] whereas in Japan good long-term results have been reported; at 1 year post-procedure 75% to 90%, at 3 years post-procedure 40% to 80%, and at 5 years post-procedure 30% to 60%.[14, 17, 32-35] Therefore, upon estimating the mortality at 1 year post-procedure in chronic





| | | | | | |
|---|---|---|---|---|---|
| S. Azuma, et al[33] (2013) | Bioprosthetic valve/Mechanical valve | 75 subjects | Operative death 5/75 (6.6%) | 74.5% | 25.5% |
| Y. Okamoto, et al[34] (2013) | Bioprosthetic valve/Mechanical valve | 40 subjects | Hospital death 2/40 (5%) | 92% | 8% |
| N. Okada, et al[14] (2015) | Bioprosthetic valve/Mechanical valve | 89 subjects | Hospital death 6/89 (6.7%) | --- | --- |
| M. Yamamura, et al[35] (2009) | Bioprosthetic valve/Mechanical valve | 24 subjects | Hospital death 3/24 (12.5%) | 79% | 21% |

---: Not applicable
*1 Kaplan-Meier estimation
*2 Calculated from the 1-year survival rate

However, since this clinical trial will be conducted in a group of patients in a poor general condition not eligible for sAVR, for PG setting the impact of differences in the patient background on the treatment results should be taken into consideration. Then, we compared the patient background in advanced medical care with which a group of patients similar to that of this clinical trial underwent TAVI at Osaka University Hospital and the patient background in the results of Japanese clinical researches shown in Table 4-3.





dialysis patients underwent sAVR, the impact of the difference in the medical environment for dialysis between Japan and Europe and the US cannot be ignored, and thus the mortality at 1 year post-procedure was estimated based on the results of Japanese clinical research.

As shown in Table 4-1, there was no difference in the results of sAVR in chronic dialysis patients by type of artificial valve (bioprosthetic or mechanical valve) ,[17, 32] for the setting of PG, regardless of bioprosthetic or mechanical, the results of both valves were used.

Table 4-1: Comparison of sAVR results in chronic dialysis patients by type of prosthetic valve

| Author (year of publication/ country) | Valve position | Implantation valve | Treatment results | | | | |
|---|---|---|---|---|---|---|---|
| | | | 30-day mortality | | 5-year survival rate *3 | | Structural valve deterioration |
| K. Tanaka, et al[32] (2009/Japan) | Aortic valve | Bioprosthetic valve (N=22) | 1/22 (4.5%)*1 | --- | 55.7 ± 7.6% | $p < 0.001$*4 | 0 subjects (FU: 42 ± 31 m) |
| | | Mechanical valve (N=51) | 4/51 (7.8%)*1 | | | | --- |
| S. Fukui, et al[17] (2012/Japan) | Aortic valve | Bioprosthetic valve (N=23) | 3/23 (13.0%)*2 | $p = 0.94$ | 35.7% | $p = 0.33$ | 0 subjects (FU: 2.3 ± 4.0 y*5) |
| | | Mechanical valve (N=15) | 2/15 (13.3%)*2 | | 29.2% | | |

---: No reports
*1 Hospital death
*2 Operative mortality (hospital death or death within 30 days post-procedure)
*3 Kaplan-Meier estimated survival rate
*4 The respective 5-year survival rate (numerical value) for bioprosthetic valve and mechanical valve were not reported. Report by Tanaka et al. suggested that compared with mechanical valve, bioprosthetic valve showed significantly lower 5-year survival rate, but there was no significant difference in the valve-related event-free rate by type of prosthetic valve ($p = 0.202$).
*5 Mean follow-up observation period in all subjects (N = 38)

The results of sAVR in Japanese chronic dialysis patients referenced for the PG setting are presented in Table 4-2. According to these Japanese clinical research reports, the mortality at 1 year post-procedure ranged between 8% and 25.5%. However, since the annual crude mortality of dialysis patients in Japan is approximately 10%,[3] based on the report by Azuma et al. and Yamamura et al., 21% to 25.5% were chosen for the mortality at 1 year post-procedure, and since the weighted mean was calculated as 24.4%, the estimated mortality at 1 year post-procedure was determined to be 25%.

Table 4-2: The results of Japanese clinical researches referenced for the PG setting

| Author (year of publication) | Type of prosthetic valve | Number of subjects | 30-day mortality | 1-year survival rate *1 | 1-year mortality *2 |
|---|---|---|---|---|---|
| K. Tanaka, et al[32] (2009) | Bioprosthetic valve/Mechanical valve | 73 subjects | Hospital death 5/73 (6.8%) | --- | --- |
| S. Fukui, et al[17] (2012) | Bioprosthetic valve/Mechanical valve | 38 subjects | Operative death 5/38 (13.2%) | --- | --- |





Table 4-3: Comparison of patient background

| | Advanced medical care | The results of Japanese clinical research reports referenced for the PG setting | | | | | |
|---|---|---|---|---|---|---|---|
| | | K. Tanaka, et al [32] | S. Fukui, et al [17] | S. Azuma, et al [33] | Y. Okamoto, et al [34] | N. Okada, et al [14] | M. Yamamura, et al [35] |
| Patient population | Chronic dialysis AS patients for whom sAVR is not indicated | Chronic dialysis AS patients for whom sAVR is indicated | | | | | |
| Treatment procedure | TAVI | sAVR | | | | | |
| Number of subjects | 24 subjects | 73 subjects | 38 subjects | 75 subjects | 40 subjects | 89 subjects | 76 subjects*1 (sAVR alone: 24 subjects) |
| Type of prosthetic valve | Bioprosthetic valve (SAPIEN/SAPIEN XT) | Mechanical valve 51 patients/Bioprosthetic valve 22 patients | Mechanical valve 23 patients/Bioprosthetic valve 15 patients | Mechanical valve 40 patients/Bioprosthetic valve 35 patients | Mechanical valve 33 patients/Bioprosthetic valve 7 patients | Mechanical valve 50 patients/Bioprosthetic valve 39 patients | Mechanical valve 14 patients/Bioprosthetic valve 10 patients |
| Age (year) | 76.7 ± 5.1 | 65.5 ± 8.3 | 69.1 ± 9.4 | 66.7 ± 8.5 | 65.8 ± 8.3 | 66 ± 8 | 63 ± 11*1 |
| Proportion of male patients | 41.7% | 60.3% | 50% | 70.7% | 77.5% | 67.4% | 60.5%*1 |
| NYHA Class III/IV | 50.0% | --- | 5.3% | --- | 85.0% | --- | --- |
| LVEF (%) | 58.8 ± 11.3 | --- | --- | 54.2 | 53 ± 13 | --- | --- |
| STS score (%) | 15.0 ± 10.7 | --- | --- | --- | --- | --- | --- |
| Length of dialysis (year) | 11.8 ± 9.3 | 12.0 ± 7.7 | 12.2 ± 9.7 | 8.1 ± 6.2 | 11.2 ± 7.8 | 12.0 ± 7.2 | 9 ± 9*1 |

*1 Including patients who received CABG and mitral valve replacement

As shown in Table 4-3, the results of comparison between the group of patients who received sAVR and the group of patients treated with TAVI showed a significant difference in the age of patients (sAVR group, < 70 years; TAVI, 76.7 years), and thus age may be the important factor in determination whether sAVR can be applied or not. Then, considering patient's age as the difference in patient background between the group of patients subject to this clinical trial and the patient group treated with sAVR shown in Table 4-2, the impact on the mortality at 1 year post-procedure was examined.

Herzog et al. reported that[15] the age of patients was a significant risk factor for long-term death in chronic dialysis patients underwent sAVR, and compared with patients aged ≤ 44 years, patient ages 45 to 64 years had a relative risk of 1.18 (95% CI: 1.08, 1.29), ages 65 to 74 had 1.45 (95% CI: 1.31, 1.60), and ≥ 75 years had 1.72 (95% CI: 1.52, 1.95). Generally the use of mechanical valve is considered for patients < 65 years, and the use of bioprosthetic valve is considered for patients ≥ 65 years, and therefore assuming that patients aged 45 to 64 for mechanical valve implantation, and 65 to 74 for bioprosthetic valve implantation in the group of sAVR, and patients ≥ 75 years are subject to this clinical trial, a maximum ratio of relative mortality risk of patients ≥ 75 years versus patients 45 to 64 years and 65 to 74 years, respectively, was determined. The results showed the relative mortality risk for patients ≥ 75 years of 1.8 times that of patients 45 to 64 years, and 1.5 times that of patients 65 to 74 years, and the weighted mean considering ratio of subjects with mechanical and bioprosthetic valves (211 : 128) in the clinical research reports shown in Table 4-2 was calculated as 1.7 times. Therefore, if the same patient group as this clinical trial receives sAVR, the mortality at 1 year post-procedure would be 42.5%, 1.7 times 25%, the estimated value from the clinical research results shown in Table 4-2, and hence the PG in this clinical trial was set as 45%.

Table 4-4: Relative mortality risk by age

| | Relative mortality risk[15] (95% CI) | Maximum ratio*1 of relative mortality risk versus ages 45 to 64 | Maximum ratio*1 of relative mortality risk versus ages 65 to 74 |
|---|---|---|---|
| ≤ 44 years | 1 | | |
| 45 to 64 years | 1.18 (1.08, 1.29) | | |
| 65 to 74 years | 1.45 (1.31, 1.60) | | |
| ≥ 75 years | 1.72 (1.52, 1.95) | 1.8 | 1.5 |

*1 The ratios were calculated using the 95% CI upper limit for ≥ 75 years and the 95% CI lower limits for 45 to 64 years and 65 to 74 years.

Therefore, when the 95% CI upper limit for the mortality at 1 year post-procedure, the primary endpoint, was lower than the PG (45%), non-inferiority of EWJ-003 therapy to the standard therapy would be verified, and this clinical trial can be considered as success.

Null hypothesis ($H_0$) and alternative hypothesis ($H_A$) are as follows:

$H_0$: Mortality at 1 year post-procedure ≥ 45%
$H_A$: Mortality at 1 year post-procedure < 45%





### 4.2.2 Clinical validity of performance goal

Subjects in this clinical trial are chronic dialysis AS patients at a higher operative risk and deemed to be inappropriate for sAVR, and by estimating the mortality at 1 year post-procedure based on the clinical research results, assuming that the same subjects receive sAVR, the PG in this clinical trial was set as 45%. However, the existing treatment for these patients is drug therapy or percutaneous balloon aortic valvuloplasty, and for evaluation of the safety and efficacy of TAVI, the study treatment, it is required that the PG is clinically acceptable even in light of the drug therapy results.

Cohort B in PARTNER-US study in non-dialysis patients deemed inappropriate for sAVR showed the mortality at 1 year post-treatment of 50.2% for 181 subjects in the drug therapy group. However, in PREVAIL-JAPAN study conducted in the similar patient group, compared with the drug therapy group in PARTNER-US study, lower baseline STS score was shown (PARTNER-US study, 11.85 ± 4.86; PREVAIL-JAPAN study, TF group 7.79 ± 3.43, TA group 10.55 ± 5.28), with a difference in patient background. Then, in order to estimate the mortality at 1 year after drug therapy in Japanese non-dialysis patients, a patient group equivalent to the interquartile range of STS score (5.35 to 11.475) in PREVAIL-JAPAN study (Japanese subset) was extracted from the drug therapy group of PARTNER-US study, and was analyzed. As a result, as shown in Table 4-5, the Kaplan-Meier estimate mortality at 1 year post-procedure in the Japanese subset of 51.2% exceeded the PG of this clinical trial (45%).

Table 4-5: Kaplan-Meier estimate mortality at 1 year post-procedure in the Japanese subset

| Mortality at 1 year post-procedure | Number of subjects | Number of events | Kaplan Meier estimate mortality | Kaplan Meier SE |
|---|---|---|---|---|
| PARTNER-US study Cohort B Drug therapy Japanese subset | 69 | 35 | 51.2% | 6.1% |

As for reports in Japan, Ohno et al. reported that 26 Japanese AS patients who received drug therapy (including 2 dialysis patients) showed the mortality at 1 year post-treatment of 53.1%[36]. That was nearly consistent with the above-mentioned PARTNER-US study results, and the mortality at 1 year post-drug therapy in Japanese non-dialysis patients was estimated as approximately 50%. Ohara et al. reported that 12 out of 16 Japanese chronic dialysis AS patients (75%) died during mean follow-up period of 32 ± 17 months,[10] and considering that among 16 patients only 2 patients received sAVR, the mortality in 14 patients who received drug therapy may be at least 71.4% (10/14). This was similar to 3-year mortality (70.7%) in 26 AS patients (including 2 dialysis patients) reported by Ohno et al., but the mean age of patients 68 ± 10 years was significantly lower than that reported by Ohno et al. (mean age 84.1 ± 5.3 years). In addition, considering that the mean patient age in the advanced medical care given at Osaka University Hospital was 76.7 ± 5.1 years, the prognosis in the drug therapy group assumed for this clinical trial can be predicted as poorer than that reported by Ohara et al., and the 1-year mortality may be over 50%.





Therefore, for evaluation of the safety and efficacy of TAVI in chronic dialysis AS patients deemed inappropriate for sAVR, the setting PG of 45% was determined to be clinically acceptable even in light of the drug therapy results.

Table 4-6: Results of drug therapy in patients with AS

| | PARTNER-US study Cohort B drug therapy group | | M. Ohno, et al.[36] | T. Ohara, et al.[10] |
|---|---|---|---|---|
| | Overall | Japanese subset | | |
| Country | US | | Japan | Japan |
| Subjects | Non-dialysis AS patients for whom sAVR is not indicated | | AS patients who refused sAVR or for whom sAVR is not indicated (including 2 dialysis patients) | Dialysis AS patients |
| Number of subjects | 181 subjects | 69 subjects | 26 subjects | 14 subjects |
| 1-year mortality | 50.2% | 51.2% | 53.1% | N/A |
| 3-year mortality | 80.9% | N/A | 70.7% | 71.4% (10/14)-85.7% (12/14) (Mean duration of FU period: 32 ± 17 months) |

## 4.3 Target Sample Size

This clinical trial aims at enrollment of 30 subjects in total. At least 2 subjects for each approach, and at least 1 subject for each size should be enrolled, so that the safety and efficacy for the TF, TA, and TAo approaches and all THV sizes (20, 23, 26, and 29 mm) could be evaluated. Enrollment will be closed when the number of patients enrolled in the study reaches the target sample size even when the above-mentioned number of patients are not ensured. Additional subjects will not be included for discontinued subjects.

Table 4-7: Target Sample Size

| Target sample size by approach | | Target Sample Size |
|---|---|---|
| Transfemoral approach | ≥ 2 subjects | A total of 30 subjects |
| Transapical approach | ≥ 2 subjects | |
| Transaortic approach | ≥ 2 subjects | |
| Target sample size by valve size | | |
| 20 mm | ≥ 1 subject | |
| 23 mm | ≥ 1 subject | |
| 26 mm | ≥ 1 subject | |
| 29 mm | ≥ 1 subject | |

<Rationales for the setting>
The sample size for this clinical trial was calculated based on the number of subjects required to verify noninferiority of the study treatment to the standard therapy by comparing the primary endpoint of all-cause mortality at 1 year post-procedure with the PG. Based on the results of the advanced medical care given in Osaka University Hospital, PREVAIL-JAPAN study, and SAPIEN XT post-marketing surveillance,





the predicted mortality at 1 year post-procedure (true value) in this clinical trial was set as 20%. As previously mentioned, the PG was set as 45%, and the number of subjects required to reject the null hypothesis ($H_0$: Mortality at 1 year post-procedure is ≥ 45%) with one-sided $\alpha = 0.05$ was calculated as 24 subjects. A sample size of 24 subjects will provide 81.1% power by one-sided Fisher's exact test. To account for the drop-out, a total of 30 subjects was determined for the target sample size for this trial. The sample size was computed using PASS 11 software.

- PG = 45%
- Predicted mortality at 1 year post-procedure (true value) = 20%
- $H_0$: Mortality at 1 year post-procedure ≥ 45%
- $H_A$: Mortality at 1 year post-procedure < 45%
- One-sided Fisher's exact test.
- Level of significance $\alpha = 0.05$

Rationale for the setting of predicted mortality at 1 year post-procedure (true value)
The mortality at 1 year post-procedure was 10.7% in the advanced medical care given at Osaka University Hospital. However, this result was observed in a single medical institution, and since the mortality at 1 year post-procedure in PREVAIL-JAPAN study conducted in non-chronic dialysis AS patients and SAPIEN XT post-marketing surveillance was 14.9% and 11.3%, respectively, the predicted mortality at 1 year post-procedure (true value) in this clinical trial should be estimated higher than these results. Therefore, maximum mortality at 1 year post-procedure in chronic dialysis patients was assumed from the results of PREVAIL JAPAN study and SAPIEN XT post-marketing surveillance. The weighted mean mortality of 11.7% was calculated for the results of PREVAIL JAPAN study and SAPIEN XT post-marketing surveillance. Kobrin et al.[29] reported that the hazard ratio of medium-term mortality by dialysis was 1.7, with the 95% CI upper limit of 2.3. Although there is a medical environmental difference for dialysis patients between in and out of Japan, the reported mean follow-up duration was 6.2 months (IQR: 2.8 to 10.8), and the impact of medical environmental difference may be small during this follow-up period. Then, assuming the maximum mortality at 1 year post-procedure of 26.9%, equivalent to 2.3 times 11.7%, the mortality at 1 year post-procedure in this clinical trial was estimated as between 10.7% and 26.9%. Since the median is determined to be 18.8%, the predicted mortality at 1 year post-procedure (true value) in this clinical trial was set as 20%.

Table 4-8: TAVI treatment results at 1 year post-procedure

| | Advanced medical care | PREVAIL JAPAN study | Post-marketing surveillance |
|---|---|---|---|
| Subjects | Chronic dialysis AS patients for whom sAVR is not indicated | Chronic dialysis AS patients for whom sAVR is not indicated | |
| Device used | SAPIEN/SAPIEN XT | SAPIEN XT | |
| Number of subjects | 24 subjects | 64 subjects | 594 subjects |
| Survival rate at 1 year post-procedure*1 | 89.3% | 85.1% | 88.7% |
| Mortality at 1 year post-procedure*2 | 10.7% | 14.9% | 11.3% |
| Weighted mean | | 11.7% | |
| The hazard ratio*3 of medium-term mortality by dialysis was taken into consideration | | 26.9% | |

*1 Kaplan-Meier estimation
*2 Calculated from the 1-year survival rate
*3 The hazard ratio of medium-term mortality by dialysis 1.7 (95% CI: 1.3, 2.3)

When the PG was established in this clinical trial, the mortality at 1 year after sAVR in Japanese chronic dialysis patients was estimated as 25%, and considering that the mortality at 1 year post-procedure in Europe and the US is approximately 40%, when the mortality in Japanese patients is counted as 1, the relative mortality risk is 1.6 for Europe and the US. If this ratio is applied to the mortality at 1 year after TAVI, the predicted mortality in this clinical trial (true value) of 20% versus 32% in Europe and the US can be determined, which was compared favorably with the results in Europe and the US as shown in Table 4-9. Therefore, setting the predicted mortality at 1 year post-procedure (true value) in this clinical trial as 20% is determined to be clinically valid.

Table 4-9: Results of TAVI in chronic dialysis patients

| Author (year of publication/country) | Device | Number of subjects | Mortality | | |
|---|---|---|---|---|---|
| | | | 30 days post-procedure | 6 months post-procedure | 1 year post-procedure |
| Advanced medical care | SAPIEN/SAPIEN XT | 24 subjects | 0% | 4.3% | 10.7% |
| M. Szerlip, et al[37] (2016/US) | SAPIEN | 43 subjects | 14.0% | 25.6% | --- |
| D.M. Kobrin, et al[29] (2015/US) | --- | 224 subjects | 13% | --- | 42.6% |
| Y. Ohno[38] (2015/Italy) | CoreValve/ SAPIEN XT | 44 subjects | 9.1% | --- | 34.1% |
| N. Dumonteil, et al[24] (2013/Europe) | CoreValve/33 subjects SAPIEN | 33 subjects | 15.2% | --- | 45.2% |
| S. Rau, et al[28] (2011/Germany) | CoreValve | 10 subjects | 0% | 20% | --- |

---: No reports

Rationale for the setting of registered number of subjects by approach

Based on the percentage of TF approach (approximately 40%) in the advanced medical care with TAVI given to chronic dialysis patients and the ratio of TA/TAo approaches of 2 : 1 in PARTNER II study, the ratio of TF, TA, and TAo approaches in this clinical trial was predicted to be 2 : 2 : 1. In comparison with this ratio, the enrollment of approximately 5 to 6 patients may be expected for TF approach; however, when





subjects are limited to chronic dialysis patients, literatures[24, 37] suggested that the ratio of TAo approach versus TA approach may be lower than the predicted ratio. In SAPIEN XT post-marketing surveillance currently underway in Japan, approximately 30% of the registered 134 subjects treated with TA approach were reported advanced calcification in the aorta. Such patients are not recommended to be treated with TAo approach. Since in chronic dialysis patients a higher morbidity may be expected due to abnormal calcium metabolism, etc., only limited number of patients may be treated with TAo approach in this clinical trial. Therefore, setting the number of subjects for each approach as at least 2 subjects was determined to be valid from the stand point of feasibility.

The manufacturer standard for introducing CoreValve[39] for which TAo approach has been already introduced in Japan, specifies at least 2 subjects for subclavian artery/direct TAo approaches, and therefore enrollment of at least 2 subjects in this clinical trial may also verify to have no technological concern in THV implantation by TAo approach. The safety of TAo approach may be comparable to that of TA also in chronic dialysis patients similarly to non-chronic dialysis patients, and therefore it was determined that a small number of subjects could verify that there is no safety concern requiring new risk evaluation in chronic dialysis patients. Therefore, also to verify the efficacy and safety of TAo approach, which was not included in the advanced medical care, in chronic dialysis patients, it was determined that setting the number of subjects as at least 2 subjects may be acceptable.

Rationale for the setting of registered number of subjects by THV size

Based on the results of SAPIEN XT post-marketing surveillance, distribution of THV in this clinical trial was predicted as 20 mm : 23 mm: 26 mm : 29 mm = 1 : 14 : 9 : 2. In comparison with this predicted ratio, about 1 to 2 subjects are expected to be registered for 20 mm. Therefore, setting the number of subjects for each size as at least 1 subject was determined to be valid from the stand point of feasibility.

### 4.4 Continued Access Registry

During a time period from the end of subject entry into the EWJ-003 analysis set until acquisition of marketing approval of the study device (EWJ-003), up to a maximum of 50 dialysis patients with severe AS requiring treatment with EWJ-003 (a maximum of 25 subjects per study site) will be included into the continued access registry. Patients eligible for this registry must be verified that they meet all inclusion criteria for the continued access registry and do not fall under any of the exclusion criteria. The duration of post-procedural follow-up observation will be for 5 years post-procedure similarly to that for the EWJ-003 analysis set and bailout treatment registry, and tests/observations required for the continued access registry will be performed. Subjects enrolled in this registry will not be included in the analysis set for the safety and efficacy evaluation of EWJ-003. For the inclusion and exclusion criteria for the continued access registry, see Sections 5.2.3 and 5.2.4, and for test/observation items, see Section 10.3.





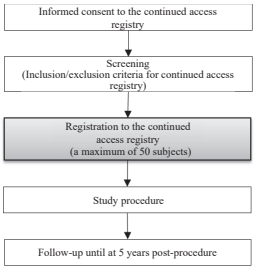



Figure 4-2: Clinical trial flow for continued access registry

<Rationales for the setting>

Once clinical symptoms, such as angina pectoris, syncope, or heart failure, manifest, the prognosis of AS is poor; the mean life expectancy of 5 years after onset of angina pectoris, 3 years after syncope, and 2 years after heart failure.[1] Furthermore, AS progresses approximately twice faster in chronic dialysis patients compared with non-dialysis patients,[6, 10] and therefore chronic dialysis patients with symptomatic severe AS should be treated as soon as possible. However, chronic dialysis patients not subject to sAVR have no choice other than palliative symptomatic treatment with drug therapy at present, because no other effective treatments are available. Therefore, on humanitarian grounds, it is required that even after completion of subject enrollment in the EWJ-003 analysis set, treatment with EWJ-003 should be continued in chronic dialysis patients. To date no concerned events from the safety and efficacy standpoints have been observed in this clinical trial, and hence it was determined that there is no problem in conducting the continued access registry and continuously providing EWJ-003 to chronic dialysis patients.

## 5 SELECTION OF SUBJECTS

### 5.1 Subjects

Subjects in this clinical trial are chronic dialysis patients with symptomatic severe AS associated with sclerosis of the native cusp of aortic valve, who are determined to be unable to undergo safe open surgical therapy, and judged EWJ-003 is the best available treatment.

### 5.2 Screening

The principal investigator or subinvestigators will give an explanation about this clinical trial to a subject,





obtain written informed consent, and check the subject's eligibility for participation in the trial. Patients eligible for this clinical trial must be verified that they meet all inclusion criteria and do not fall under any of the exclusion criteria.

Each study conducting medical institution must create and maintain subject enrolment log.

#### 5.2.1 Inclusion criteria

Candidates for this study must meet all of the following inclusion criteria:

(1) Patients determined by the heart team to be unable to undergo safe open surgical therapy, and judged EWJ-003 is the best available treatment. Specifically, considering the followings as risk factors, the risk should be comprehensively determined.
- Porcelain aorta
- History of mediastinal radiotherapy
- History of mediastinitis
- Remarkable thoracic deformity
- Previous open heart surgery or coronary-artery bypass grafting
- Chronic obstructive pulmonary disease

(2) Patient has senile degenerative AS with one of the following echocardiographic criteria. Measurement of aortic valve area (AVA) at baseline must be acquired within 60 days prior to the study procedure.
a. Mean pressure gradient ≥ 40 mmHg
b. Aortic flow velocity ≥ 4.0 m/s
c. AVA at baseline ≤ 1.0 $cm^2$
d. AVA index ≤ 0.6 $cm^2/m^2$

(3) Patient has symptoms associated with AS ≥ NYHA class II.

(4) The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical sites.

(5) The subject and the investigator agreed to comply with all required post-procedural follow-up visits.

(6) Patient has been on dialysis (hemodialysis or peritoneal dialysis) in stable condition for ≥ 3 months.

(7) Patient has any one of the following native aortic valve annulus sizes as measured by transesophageal echocardiography (TEE) or 3D- computed tomography (CT).
a. Native annulus size ≥ 16 mm and ≤ 28 mm by TEE
b. Native annulus area ≥ 273 $mm^2$ and ≤ 683 $mm^2$ by 3D-CT
c. Area-derived diameter ≥ 18.6 mm and ≤ 29.5 mm by 3D-CT

(8) Patient is verified by the Case Review Process that the treatment with EWJ-003 is appropriate for the patient.

<Rationales for the setting>

The inclusion criteria for this clinical trial were set up in reference to the inclusion criteria for a US clinical study of the study device PARTNER II study, Japanese clinical studies of previous generation SAPIEN XT PREVAIL JAPAN study (EW-P-001) and PREVAIL-20 JAPAN study (EW-P-002), and advanced medical care that evaluated TAVI with SAPIEN and SAPIEN XT in chronic dialysis patients. The rationales for the setting of individual inclusion criteria are as shown in the followings:

| | |
|---|---|
| (1) | Set up based on the current indications for EWJ-003 in Japan. |
| (2) | As the diagnostic criteria for severe AS for which EWJ-003 therapy is indicated, set up based on the American College of Cardiology (ACC)/American Heart Association (AHA) guideline[20] and Japanese Guidelines for Surgical and Interventional Treatment of Valvular Heart Disease.[12] |
| (3) | Since the ACC/AHA guideline[20] and Japanese Guidelines for Surgical and Interventional Treatment of Valvular Heart Disease[12] recommend aortic valve replacement for patients with symptomatic severe AS, similarly to the past clinical trials, symptomatic was defined as NYHA Class II and over. |
| (4) | Set up to ensure human rights of subjects. |
| (5) | Set up to ensure the quality of trial. |
| (6) | Guidelines for Clinical Evaluation of Therapeutic Drugs for Renal Anemia issued on September 30, 2011[40] (Notification No.0930-2 of the Evaluation and Licensing Division, PFSB) recommend that patients who have past at least 3 months after introduction of dialysis and in a stable condition be included in clinical trials. In order to avoid difficulty in data interpretation for evaluation of the safety and efficacy of EWJ-003 therapy in chronic dialysis patients, also this clinical trial will include dialysis patients who have past at least 3 months after introduction of dialysis and in a stable condition. In addition, the recommendations for valvular disease surgery in dialysis patients in Guidelines for Surgical and Interventional Treatment of Valvular Heart Disease[12] do not classify the type of dialysis (hemodialysis or peritoneal dialysis), and based on the reports that there was no difference in the mortality at 1 year post-procedure between hemodialysis patients and peritoneal dialysis patients[41] and that both hemodialysis and peritoneal dialysis could be adequately managed for periprocedural control,[42] both hemodialysis and peritoneal dialysis patients could be included. |
| (7) | Set up based on the applicable aortic annulus size of EWJ-003. |
| (8) | Set up because upon inclusion in this clinical trial a patient should be verified by the Case Review Process that the treatment with EWJ-003 is appropriate for the patient. |

### 5.2.2 Exclusion criteria

Candidates for this clinical trial must not fall under any one of the following exclusion criteria:





| | |
|---|---|
| (1) | Patient has an evidence of an acute MI within 1 month (30 days) prior to the study procedure. Acute MI is defined as; Q wave MI, or non-Q-wave MI with elevation of creatine kinase MB isoenzyme (CK-MB) or troponin, together with the evidence of myocardial ischemia with at least one of the following findings:<br>• Symptoms of ischemia<br>• Electrocardiogram (ECG) changes indicative of new ischemia (ST-T changes, left bundle-branch block [LBBB])<br>• Imaging evidence of a new loss of viable myocardium or new wall motion abnormality. |
| (2) | Patient has a congenital unicuspid or bicuspid. Or patient has a non-calcified aortic valve. |
| (3) | Patient has severe aortic valve incompetence. |
| (4) | Patient has severe mitral valve incompetence. |
| (5) | Patient has an evidence of any therapeutic invasive cardiac procedures within 30 days prior to the study procedure. However, implantation of a permanent pacemaker or balloon valvuloplasty for bridging to procedure after a qualifying echocardiography are excluded. |
| (6) | Patient with planned concomitant surgical or transcatheter ablation for atrial fibrillation. |
| (7) | Patient has pre-existing prosthetic valve in any position. |
| (8) | Patient is at a high risk of bleeding, difficult to have appropriate treatment, or unable to receive appropriate anticoagulation or antiplatelet therapy.<br>• Leukopenia (white blood cell < 3,000 cells/$mm^3$)<br>• Thrombocytopenia (platelet < 50,000 cells/$mm^3$)<br>• Bleeding diathesis or coagulopathy<br>• Active gastro-intestinal ulceration, or upper gastro-intestinal bleeding within the past 3 months<br>• Refuse blood transfusion<br>• Receiving anticoagulant and/or antiplatelet medication and can't stop them for the study procedure<br>• Concluded by investigator that appropriate anticoagulation or antiplatelet therapy is difficult for any other reasons |
| (9) | Patient has untreated clinically significant coronary artery disease requiring revascularization. |
| (10) | Patient has hemodynamic instability requiring inotropic support or mechanical heart assistance. Patient has respiratory instability requiring mechanical ventilation. |
| (11) | Patient requires an emergency surgery for any reason. |
| (12) | Patient has hypertrophic cardiomyopathy with or without obstruction. |
| (13) | Patient has severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20%. |
| (14) | Patient has echocardiographic evidence of intracardiac mass, thrombus, or vegetation. |
| (15) | Patient has hypersensitivity to or a known contraindication of heparin and/or aspirin, which cannot be adequately pre-medicated. Patient has a known hypersensitivity to contrast media. |
| (16) | Patient has hypersensitivities to cobalt, chromium, nickel, molybdenum, titanium, manganese, |





| | |
|---|---|
| | silicon, or polymeric materials. |
| (17) | Patient has had a cerebrovascular accident or transient ischemic attack within 6 months prior to the study procedure. Except cases with an event associated with AS. |
| (18) | Patient with poorly controlled blood pressure. |
| (19) | Patient has serum albumin < 3.0 g/dL or body mass index (BMI) < 18. |
| (20) | Patient has uncontrollable diabetes mellitus. |
| (21) | Patient has active bacterial endocarditis or other active infection. |
| (22) | Patient has life expectancy < 12 months due to pre-operative non-cardiac comorbidity (e.g., cancer, chronic liver disease). |
| (23) | Currently participating in an investigational drug or another device study. [Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.] |
| (24) | Cardiovascular surgeons and cardiologists concluded that the patient is inappropriate for participating in this trial. |
| | < TF approach> |
| (25) | Patient has significant tortuous aorta, diseases including abdominal aortic or thoracic aneurysm, or significant atheroma in the femoral artery or iliac artery that would prevent from proper placement of delivery system. |
| (26) | Patient has iliofemoral vessel characteristics that would preclude safe placement of 14F or 16F introducer sheath such as severe obstructive calcification and severe tortuosity, or minimum average vessel size less than 5.5 mm (6.0 mm for 16F introducer sheath). |

<Rationales for the setting>

The exclusion criteria for this clinical trial were set up in reference to the inclusion criteria for a US clinical study of the study device PARTNER II study, Japanese clinical studies of previous generation SAPIEN XT PREVAIL JAPAN study (EW-P-001) and PREVAIL-20 JAPAN study (EW-P-002), and advanced medical care that evaluated TAVI with SAPIEN and SAPIEN XT in chronic dialysis patients. The rationales for the setting of individual exclusion criteria are as shown in the followings:

| | |
|---|---|
| (1) | The infarction site after onset of MI is vulnerable due to necrosis, and it is difficult to tolerate increased cardiac stress, which may induce myocardial rupture or papillary muscle rupture. Therefore, considering the safety and the impact of higher incidence of serious adverse events (SAEs) on evaluation of the study device, these patients were excluded. |
| (2) | Since patients with congenital unicuspid or bicuspid may have a theoretical risk of paravalvular regurgitation and expansion failure of the device, these patients were excluded. Patients with no calcification were also excluded, as the THV may not be properly fixated. |
| (3) | AS patients complicated with severe aortic valve incompetence are expected to have very poor |





| | |
|---|---|
| | morbidity of the cusp and with significant calcification, leading to difficulty in predilatation and THV implantation. |
| (4) | Disruption of blood flow may occur in patients complicated with severe mitral valve incompetence due to released AS by the study procedure. |
| (5) | Excluded because of the possible impact on proper evaluation of the study device. If pacemaker implantation, and balloon aortic valvuloplasty was performed as a role of bridging before the study procedure, the patient could be included in this clinical trial. However, since the mortality risk after treatment with an implantable cardioverter defibrillator in chronic dialysis patients is significantly high,[43] patients with implantable cardioverter defibrillator were excluded. |
| (6) | When surgery for atrial fibrillation is simultaneously given, interpretation of data may be difficult and that affects proper evaluation of the study device. In addition, it has been reported that concomitant procedure with sAVR in chronic dialysis patients was a significant risk factor for periprocedural death[44], and it was suggested that also in the treatment with EWJ-003 concomitant procedure may be a risk factor for outcome of death. Therefore, from the endurance and safety standpoints, concomitant procedure was excluded. Patients with scheduled coronary revascularization at the same time were excluded by the exclusion criterion (9). |
| (7) | Excluded because of the possible impact on proper evaluation of the study device. |
| (8) | Excluded because of a higher bleeding risk, and bleeding may become severer due to the use of anticoagulant/anti-platelet drug, and some cases it may lead to death. |
| (9) | If severe coronary artery stenosis coexists, left ventricular myocardial ischemia may widespread during the procedure, which may lead to cardiogenic shock, severe arrhythmia, and cardiac arrest. If coronary revascularization is concomitantly or perioperatively performed, which may lead to a risk of significant complication. This risk may affect proper evaluation of the study device. |
| (10) | In patients who have hemodynamic instability requiring catecholamine inotropic agents including dobutamine and dopamine or mechanical heart assistance, it is difficult to implant the THV. In addition, patients who have respiratory instability requiring ventilator have a higher risk of intraoperative/post-operative complication, and hence these patients were excluded from the standpoint of safety. |
| (11) | Excluded from the safety standpoint, because of a high probability of incidence of SAEs. |
| (12) | Improvement by implantation of the study device cannot be expected in patients with hypertrophic cardiomyopathy. |
| (13) | In patients with significantly impaired left ventricular function, often the left ventricular myocardium has an irreversible change, and even after implantation of the study device it will be difficult to evaluate hemodynamics appropriately. In addition, likely to cause periprocedural death, and excluded from the endurance and safety standpoints. |
| (14) | It may be released during operations in the heart, causing embolism. |
| (15) | Patients intolerance to the anticoagulant/antiplatelet drugs that are recommended in this clinical trial, and patients who have a known hypersensitivity to contrast agents are generally |

contraindicated for TAVI.

(16) Patient has a known hypersensitivity to the components of the study device were excluded.

(17) Patients who have a neurological event are deemed unable to be evaluated properly for the study device.

(18) Guidelines for treatment of hypertension by The Japanese Society of Hypertension[45] classify dialysis patients in the high risk group. Since it has been reported that sudden hypotension (systolic pressure ≥ 30 mmHg) and orthostatic hypotension after dialysis correlate with poor prognosis[46], patients complicated with abnormal blood pressure that cannot be appropriately controlled were excluded.

(19) It is known that hypoalbuminemia in dialysis patients is a factor for difficulty in maintenance of blood pressure[47], and it has been reported that hemodialysis patients with serum albumin < 3.0 g/dL, compared with those with ≥ 3.0 g/dL, have a significantly higher mortality risk.[48] In addition, it has been reported that long-term malnutrition can be suggested in patients with BMI < 18, and low BMI in dialysis patients after sAVR can be a significant risk factor for long-term death.[49] Also 2012 Critical limb ischemia field review WG report[50] recommends that if dialysis patients complicated with critical limb ischemia are included in a clinical trial for evaluation of the safety and efficacy of medical devices for revascularization of critical limb ischemia, maintenance dialysis patients with hypoalbuminemia (< 3.0 g/dL) or low BMI (< 18) be excluded.

(20) It was reported that diabetic nephropathy is a significant risk factor for long-term mortality in sAVR in chronic dialysis patients,[15] suggesting that also in the treatment with EWJ-003 diabetic complication may be a risk factor for outcome of death. On the other hand, since it has been reported that good glycemic control correlates with prognosis of dialysis patients complicated with diabetes mellitus, especially reduced cardiovascular mortality,[51] patients complicated with poorly controlled blood glucose diabetes were excluded from this clinical trial.

(21) These patients are at a higher risk of post-procedural adverse events (AEs) including sepsis, and dialysis patients are susceptible to infections, and therefore considering the safety they were excluded.

(22) The patient is more likely to discontinue the clinical trial prior to completion of long-term follow-up observation.

(23) Involvement in other clinical trial may affect evaluation of the study device in this clinical trial.

(24) This was set up to include a group of patients with appropriate background in this clinical trial after considering risks versus benefits of treatment with EWJ-003.

(25) It is difficult to deliver the THV, and patients with concurrent aneurysm are at a very high risk of aneurysm rupture.

(26) When the THV is implanted via TF approach, 14F or 16F introducer sheath should be used, and therefore patients with difficulty in safe implantation of sheath were excluded.





### 5.2.3 Inclusion criteria for continued access registry

Candidates for the continued access registry must meet all of the following inclusion criteria:

(1) Patients determined by the heart team to be unable to undergo safe open surgical therapy, and judged EWJ-003 is the best available treatment. Specifically, considering the followings as risk factors, the risk should be comprehensively determined.
- Porcelain aorta
- History of mediastinal radiotherapy
- History of mediastinitis
- Remarkable thoracic deformity
- Previous open heart surgery or coronary-artery bypass grafting
- Chronic obstructive pulmonary disease

(2) Patient has senile degenerative AS with one of the following echocardiographic criteria. Measurement of AVA at baseline must be acquired within 60 days prior to the study procedure.
a. Mean pressure gradient ≥ 40 mmHg
b. Aortic flow velocity ≥ 4.0 m/s
c. AVA at baseline ≤ 1.0 $cm^2$
d. AVA index ≤ 0.6 $cm^2/m^2$

(3) Patient has symptoms associated with AS ≥ NYHA class II.

(4) The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the IRB of the respective clinical sites.

(5) The subject and the investigator agreed to comply with all required post-procedural follow-up visits.

(6) Patient on maintenance dialysis (hemodialysis or peritoneal dialysis).

(7) Patient has any one of the following native aortic valve annulus sizes as measured by TEE or 3D-CT.
a. Native annulus size ≥ 16 mm and ≤ 28 mm by TEE
b. Native annulus area ≥ 273 $mm^2$ and ≤ 683 $mm^2$ by 3D-CT
c. Area-derived diameter ≥ 18.6 mm and ≤ 29.5 mm by 3D-CT





<Rationales for the setting>

For patients deemed possible for safe treatment with EWJ-003, but do not meet all of the inclusion criteria described in Section 5.2.1, and therefore no chance of treatment, to make it possible to receive treatment with EWJ-003 on humanitarian grounds, for the continued access registry, the following changes were made to the inclusion criteria described in Section 5.2.1.

Table 5-1: Changes made to inclusion criteria

| Inclusion criteria described in Section 5.2.1 | Inclusion criteria for continued access registry | Reason for change |
|---|---|---|
| (6) Patient has been on dialysis (hemodialysis or peritoneal dialysis) in stable condition for ≥ 3 months. | (6) Patient on maintenance dialysis (hemodialysis or peritoneal dialysis). | Based on the Guidelines for Clinical Evaluation of Therapeutic Drugs for Renal Anemia,[40] unstable patients at early stage of dialysis were excluded for appropriate evaluation of the safety and efficacy of EWJ-003. However, the continued access registry is not aiming at evaluation of the efficacy and safety of EWJ-003, and therefore not limiting a history of dialysis, and whether or not the patient can be treated with EWJ-003 can be determined taking individual patient's condition and safety into consideration, this change was made. |
| (8) Patient is verified by the Case Review Process that the treatment with EWJ-003 is appropriate for the patient. | (Deleted) | Because in the continued access registry case review is not mandatory, this criterion was deleted. |

### 5.2.4 Exclusion criteria for continued access registry

Candidates for the continued access must not fall under any one of the following exclusion criteria:

(1) Patient has an evidence of an acute MI within 1 month (30 days) prior to the study procedure. Acute MI is defined as; Q wave MI, or non-Q-wave MI with elevation of CK-MB or troponin, together with the evidence of myocardial ischemia with at least one of the following findings:
- Symptoms of ischemia
- ECG changes indicative of new ischemia (ST-T changes, LBBB)
- Imaging evidence of a new loss of viable myocardium or new wall motion abnormality.

(2) Patient has a congenital unicuspid or bicuspid. Or patient has a non-calcified aortic valve.

(3) Patient has severe aortic valve incompetence.

(4) Patient has severe mitral valve incompetence.

(5) Patient has an evidence of any therapeutic invasive cardiac procedures within 30 days prior to the study procedure. However, implantation of a permanent pacemaker or balloon valvuloplasty for bridging to procedure after a qualifying echocardiography are excluded.

(6) Patient with planned concomitant surgical or transcatheter ablation for atrial fibrillation.

(7) Patient has pre-existing prosthetic valve in any position.





(8) Patient is at a high risk of bleeding, difficult to have appropriate treatment, or unable to receive appropriate anticoagulation or antiplatelet therapy.
- Leukopenia (white blood cell < 3,000 cells/$mm^3$)
- Thrombocytopenia (platelet < 50,000 cells/$mm^3$)
- Bleeding diathesis or coagulopathy
- Active gastro-intestinal ulceration, or upper gastro-intestinal bleeding within the past 3 months
- Refuse blood transfusion
- Receiving anticoagulant and/or antiplatelet medication and can't stop them for the study procedure
- Concluded by investigator that appropriate anticoagulation or antiplatelet therapy is difficult for any other reasons

(9) Patient has untreated clinically significant coronary artery disease requiring revascularization.

(10) Patient has hemodynamic instability requiring mechanical heart assistance. Patient has respiratory instability requiring mechanical ventilation.

(11) Patient requires an emergency surgery for any reason.

(12) Patient has hypertrophic cardiomyopathy with or without obstruction.

(13) Patient has severe ventricular dysfunction with LVEF < 20%.

(14) Patient has echocardiographic evidence of intracardiac mass, thrombus, or vegetation.

(15) Patient has hypersensitivity to or a known contraindication of heparin and/or aspirin, which cannot be adequately pre-medicated. Patient has a known hypersensitivity to contrast media.

(16) Patient has hypersensitivities to cobalt, chromium, nickel, molybdenum, titanium, manganese, silicon, or polymeric materials.

(17) Patient has had a cerebrovascular accident or transient ischemic attack within 6 months prior to the study procedure. Except cases with an event associated with AS.

(18) Patient with poorly controlled blood pressure.

(19) Patient has serum albumin < 2.8 g/dL or BMI < 16.

(20) Patient has uncontrollable diabetes mellitus.

(21) Patient has active bacterial endocarditis or other active infection.

(22) Patient has life expectancy < 12 months due to pre-operative non-cardiac comorbidity (e.g., cancer, chronic liver disease).

(23) Currently participating in an investigational drug or another device study. [Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.]

(24) Cardiovascular surgeons and cardiologists concluded that the patient is inappropriate for participating in this trial.

<TF approach>

(25) Patient has significant tortuous aorta, diseases including abdominal aortic or thoracic aneurysm, or significant atheroma in the femoral artery or iliac artery that would prevent from proper placement of delivery system.

(26) Patient has iliofemoral vessel characteristics that would preclude safe placement of 14F or 16F introducer sheath such as severe obstructive calcification and severe tortuosity, or minimum average vessel size less than 5.5 mm (6.0 mm for 16F introducer sheath).

<Rationales for the setting>

For patients deemed possible for safe treatment with EWJ-003, but fall under one of the exclusion criteria described in Section 5.2.2, and therefore no chance of treatment, to make it possible to receive treatment with EWJ-003 on humanitarian grounds, for the continued access registry, the following changes were made to the exclusion criteria described in Section 5.2.2.

Table 5-2: Changes made to exclusion criteria

| Exclusion criteria described in Section 5.2.2 | Exclusion criteria for continued access registry | Reason for change |
|---|---|---|
| (10) Patient has hemodynamic instability requiring inotropic agents or mechanical heart assistance. Patient has respiratory instability requiring mechanical ventilation. | (10) Patient has hemodynamic instability requiring mechanical heart assistance. Patient has respiratory instability requiring mechanical ventilation. | Some patients need prophylactic inotropic agents before and during dialysis for smooth dialysis although the hemodynamics does not interfere with safe implantation of EWJ-003, and therefore irrespective of with or without inotropic agents, whether or not the patient can be treated with EWJ-003 can be determined taking individual patient's condition and safety into consideration, this change was made. |
| (19) Patient has serum albumin < 3.0 g/dL or BMI < 18. | (19) Patient has serum albumin < 2.8 g/dL or BMI < 16. | For the continued access registry, the exclusion criteria were set up, based on the serum albumin 2.8 g/dL, the physiological reference value that induces edema associated with decreased visceral protein mass due to malnutrition,[52] and BMI 16, the reference value that causes a significantly higher mortality risk in Japanese older adults.[53] |

## 5.3 Case Review Process

The results of screening conducted by the heart team in the study site confirmed that all of the inclusion criteria were satisfied, and none of the exclusion criteria were met, and patients who were deemed eligible for this clinical trial will be eventually determined for their eligibility by the case review. The case review should be conducted by at least one investigator and/or subinvestigator from a study site other than the screening site, and when eligibility of the patient is approved, the patient can be registered as a subject in this clinical trial. For detailed case review procedure, see the "Japan Case Review Procedure."





Case review is not mandatory in the continued access registry. When the results of screening conducted by the heart team in the study site confirmed that all of the inclusion criteria were satisfied, and none of the exclusion criteria were met, the patient is regarded as eligible for this clinical trial. When a case review is performed as necessary, it should be based on the same procedure as that of the main clinical trial.

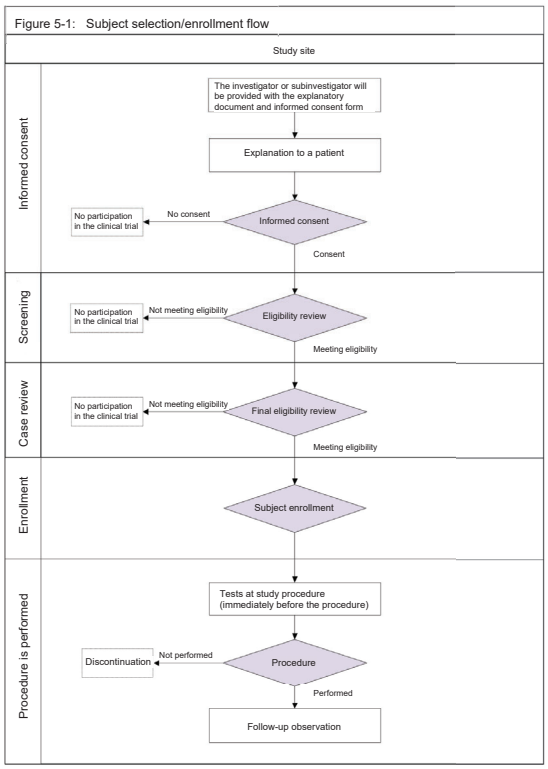
## 5.4 Subject Enrollment

For patients who were eventually determined to be eligible for this clinical trial by case review, enrollment in this clinical trial should be completed by the document describing the patient's eligibility. For the continued access registry, patients deemed eligible for this registry by screening will be enrolled in this registry by the start of study procedure (at the time point when an invasion such as an incision is made on the access site). For the subject selection/enrollment flow, see Figure 5-1.





Figure 5-1: Subject selection/enrollment flow




Note: Case review is not mandatory in the continued access registry. Patients deemed eligible for the continued access registry by screening conducted by the heart team of the study site will be regarded as registered in this registry by the start of study procedure (at the time point when an invasion such as an incision is made on the access site). Even after case review, the patient will be regarded as completed registration in this registry by the start of study procedure.





# 6 CONSIDERATIONS CONCERNING SUBJECT'S INFORMED CONSENT

Subject's informed consent should be obtained in compliance with the followings:

(1) The principal investigator or subinvestigators will give an explanation about this clinical trial to subjects, using written patient information approved by the IRB and other appropriate documents, and obtain written informed consent to participation in this clinical trial voluntarily signed by the subjects.

(2) Before informed consent may be obtained, the principal investigator or subinvestigators should provide the subject with ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial.
The subject should fully understand the contents of the clinical trial, and then sign or place name and a seal and date the informed consent form that describes consent to participation in this clinical trial. The principal investigator or subinvestigators who provided an explanation to the subject should sign or place name and a seal and date the informed consent form. However, if a subject is unable to read the written patient information due to physical problem and so on, but can understand the contents of the written patient information given orally or other communication means, an impartial witness should be present during the informed consent discussion. In such a case, in addition to the subject, the witness should sign or place name and a seal and date the informed consent form. When a study staff provided a supplemental explanation, also the study staff should sign or place name and a seal and date the informed consent form.

(3) The principal investigator, subinvestigators, or study staff (hereinafter referred to as "investigators") should enter the date of subject's written informed consent, and if a witness is required, the date of witness, in the electronic case report form (eCRF).

(4) The principal investigator or subinvestigators must not perform tests for the purpose of this clinical trial until after acquisition of written informed consent. The principal investigator or subinvestigators should confirm whether or not the subject has other personal physician, and after an agreement with the subject, inform the personal physician of the subject's participation in this clinical trial. If the subject may be newly consulting other hospital/department after participation in this clinical trial, the principal investigator or subinvestigators should instruct the subject to inform the new hospital/department of participation in this clinical trial.

(5) If information becomes available that may be relevant to the subject's willingness to continue participation in the trial, the principal investigator or subinvestigators should inform the subject in a timely manner, confirm as to whether or not the subject is willing to continue the trial, and record it in the medical records, etc.

(6) If the principal investigator considers that the written patient information should be revised, the

written patient information should be revised promptly based on the relevant information. The principal investigator should notify the director of the study site of the revised written patient information, and obtaining IRB's approval. After approval, the principal investigator or subinvestigators should obtain the subject's voluntarily signed written consent to continued participation in this clinical trial. If a witness is required, follow (2).

(7) The investigators should enter the date of subject's written informed reconsent, and if a witness is required, the date of witness, in the eCRF. Further, if legally acceptable representative is required, the investigators should enter the date of consent given by the legal representative in the eCRF.

(8) The principal investigator or subinvestigators will provide the subject with a copy of signed or name and seal placed informed consent form and written information. The original informed consent form signed or name and a seal placed should be retained by the study site.

# 7 TREATMENT OF SUBJECTS

## 7.1 Baseline Tests

The subjects enrolled in this clinical trial will receive tests to obtain baseline values before the procedure, so as to confirm the impact of the THV on patients, compared with follow-up observation values after the procedure. These test results will be entered in eCRFs and will be used for determination of eligibility of the subjects. If there are some data of tests carried out within the permissible time range of baseline tests available, even the results of tests carried out before acquisition of informed consent or to confirm subject's eligibility may be used as baseline data.

For baseline test/observation items and timing, see Sections 10.1 and 10.2.1.

## 7.2 Study Procedure

In this clinical trial, the investigational valve may be implanted by either TF, TA, or TAo approach. However, TF approach should be the first line of treatment, and when TF approach is difficult to perform, carefully examine the subject's clinical and anatomical characteristics, and then select appropriate access site (TA or TAo approach).

For deployment of the THV, the balloon should be inflated at a nominal volume (see Section 3.2 Table 3-2), and if dilatation at a nominal volume is impossible for medical reasons, the subject should be included in the bailout treatment registry (see Section 7.4 "Bailout Treatment Registry"). In the continued access registry, irrespective of whether the THV was implanted at a nominal volume or not, subjects who received the study procedure will be included in this registry. For preparation of study device, THV rinsing, and detailed implantation procedure, see Attachment 2 "Instructions for Use." In order to ensure and protect the





safety of the subjects, the sponsor should witness all procedures as much as possible and consider to be able to respond to questions about the study device and study procedure.

If severe aortic valve regurgitation is observed after implantation of the THV, a valve-in-valve procedure may be performed. When a valve-in-valve procedure is required, as a general rule, the study device should be used. Since sufficient evidence has not been obtained for the safety and efficacy of the valve-in-valve procedures, a physician who performs implantation should carefully select the size and perform the implantation procedure.

## 7.3 Post-procedural Follow-up Observation

All subjects for whom the THV was implanted and maintained at the time point when the subject left the operetaion room should undergo the 5-year post-procedural follow-up observation specified in the protocol. For study discontinuation subjects without implantation of the investigational valve for the reasons that the procedure was switched to surgery, or already approved TAVI bioprosthetic valve was implanted, participation in this trial should be discontinued at the time point, and follow-up observation will not be required thereafter.

For the test/observation items and timing in the post-procedural follow-up observation, see Section 10.

## 7.4 Bailout Treatment Registry

Patients in whom deployment of the THV by balloon dilatation at a nominal volume was impossible for a medical reason will be regarded as bailout cases, and these cases will be included in the bailout treatment registry at the end of study procedure. The bailout cases will be enrolled separately from the target sample size of this trial (30 subjects), and will not be included in the analysis set for the safety and efficacy evaluation of EWJ-003. The same post-procedural follow-up observation will be performed as that for subjects with successful valve implant procedure at a nominal volume, and the follow-up observation will be performed for up to 5 years post-procedure.

In the continued access registry, irrespective of whether the THV was implanted at a nominal volume or not, subjects who received the study procedure will be included in this registry.





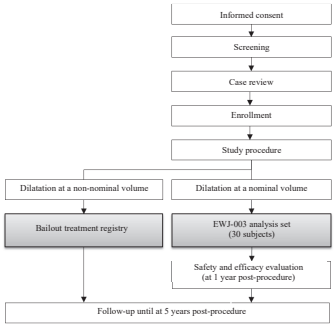



Figure 7-1: Bailout treatment registry treatment flow





# 8 CONCOMITANT THERAPY

## 8.1 Anticoagulation/Antiplatelet Therapy

As a general rule, the principal investigator or subinvestigators should provide anticoagulation/antiplatelet regimen in accordance with Table 8-1. However, considering individual subject's clinical circumstance including validity of contraindications for a subject, the dosage, concomitant drugs, timing of administration, and duration of administration should be decided, at the discretion of the primary physician. For example, if a subject with atrial fibrillation receives warfarin potassium, or a subject with obstructive arteriosclerosis or a subject with a stent implanted in the peripheral blood vessel or coronary artery (including bypass graft) is on an antiplatelet agent other than aspirin, taking continuous use into consideration, anticoagulation/antiplatelet therapy should be provided. Therefore, when anticoagulation/antiplatelet therapy different from those recommended in Table 8-1 (e.g., ticlopidine hydrochloride and clopidogrel sulfate) is given, the protocol deviation is not applicable.

Chronic dialysis patients, compared with non-dialysis patients, have a strong bleeding tendency, often leading to difficulty in hemostasis, patients on antiplatelet drugs and/or anticoagulant (excluding anticoagulant at dialysis) before the procedure, these drugs should be discontinued at least 14 days before the procedure as a general rule, so that the effect of these drugs fades away.

Table 8-1: Recommended anticoagulation/antiplatelet regimen

| Drug | Pre-procedure | At procedure | Post-procedure |
|---|---|---|---|
| Heparin | None | 5000 IU/dose, then heparin will be given to achieve and maintain ACT ≥ 250 sec as needed | None |
| Aspirin | None | None | 75 - 100 mg/day, once daily continued indefinitely |

[Pre-procedural antiplatelet therapy]
Considering bleeding risk, pre-procedural anticoagulation/antiplatelet therapy will not be given. However, if a platelet function inhibitory action is required, aspirin, etc. should be carefully administered in accordance with the package insert.

[Anticoagulant therapy at procedure]
After intravenous administration of heparin 5000 IU/dose, heparin will be given to achieve and maintain activated clotting time (ACT) ≥ 250 seconds as needed throughout the course of the procedure. Monitor the ACT at regular intervals, and record it in the source document.

[Post-procedural antiplatelet therapy]
After the procedure, aspirin monotherapy will be given at a dose of 75 to 100 mg/day for an indefinite period after study procedure.

<Rationales for the setting>
Considering bleeding risk related to the procedure, irrespective of the implantation approach, pre-procedural antiplatelet therapy will not be given. For the anticoagulant therapy during procedure, in addition to thromboprophylaxis, in order to inhibit enhancement of the blood coagulation system induced by damage on the vascular inner wall and prevent consumption of the blood coagulation factor, heparin will be administered. As for post-procedural antiplatelet therapy, compared with non-dialysis patients, dialysis patients have a higher trend toward bleeding, and therefore similarly to the antiplatelet therapy given in the advanced medical care at Osaka University Hospital, administration of aspirin single-agent for indefinite period was recommended. Aspirin is an agent that undergoes hepatic metabolism, and therefore the pharmacokinetics of these antiplatelet drugs is not affected in dialysis patients with impaired renal excretion.

### 8.2 Prophylactic Administration of Antibiotics

An antibiotic agent will be administered to the subjects who undergo implantation procedure of the study device immediately before the start of the procedure. Regardless of the type of antibiotic agent, considering the use status of antibiotic agents at each study site, possible drug-resistant bacteria, and an impact on subject's renal function, antibiotic agents should be chosen. If methicillin-resistance is suspected, consider the use of vancomycin.

<Rationales for the setting>
In the subjects receiving implantation of the study device, incidence of endocarditis associated with infection may be fatal and therefore the subjects should be prophylactically treated for infections per the recommendations by the AHA[54] prior to the procedure.

### 8.3 Precautions for Concomitant Drugs

The following concomitant drugs should be carefully used, and the concomitant use should be avoided as much as possible. When the concomitant use is necessary, concomitant use other than single use should be avoided.

- Non-steroidal anti-inflammatory drug (indomethacin, etc.)
- Steroids, tacrolimus preparations, and other immunosuppressants

<Rationales for the setting>
Since non-steroidal anti-inflammatory drugs may cause interactions with aspirin (enhancing), concomitant use other than single use in necessary cases should be avoided. Since steroids, tacrolimus preparations, and other immunosuppressants may affect the immune system, concomitant use other than single use in





necessary cases should be avoided.

### 8.4 Periprocedural Hemodialysis

Perform periprocedural hemodialysis in accordance with the following recommendations:

[Pre-procedural hemodialysis]
- For hemodialysis patients, perform hemodialysis until achievement of this dry weight on the day before study procedure as a general rule.
  Do not change the anticoagulant therapy.
- For peritoneal dialysis patients, continue peritoneal dialysis as usual until the day before study procedure.

[Post-procedural hemodialysis]
- Considering post-procedural hemodynamics, resume dialysis at the discretion of the investigator.
- In case of the hemodialysis, it is recommended to use anticoagulant with shorter half-life (e.g. nafamostat mesilate) to reduce bleeding risk.
- Do not change dialysis conditions until 1 year post-procedure as a general rule. However, the dialysis conditions may be changed if it is based on the medical judgement.

### 8.5 Other Drugs/Therapies

Drugs or therapies previously used before procedure in the treatment of the primary disease should be discontinued as a general rule, unless they are used also for pre-procedural complication. Drugs or therapies used before procedure in the treatment of pre-procedural complication should be maintained as much as possible. This does not apply to the cases where it is used for an AE or aggravated primary disease.

<Rationales for the setting>
Since treatments of the primary disease may affect the evaluation of this clinical trial, the use of these drugs or therapies should be discontinued as a general rule. If the same treatment is maintained from prior to the procedure, other treatments of complication may not affect the evaluation of this clinical trial, considering well-being of the trial subjects, these could be concomitantly used.

### 8.6 Precautions for Concomitant Drugs/Concomitant Therapy and Input Procedure in Electronic Case Report Forms

#### 8.6.1 Anticoagulant/antiplatelet drugs and antibiotics

Observe anticoagulant/antiplatelet drug (excluding anticoagulant at dialysis) from 7 days prior to the day of





the procedure (counting the procedure day as Day 0) throughout the observation period, and for antibiotics from 7 days prior to the procedure day (counting the procedure day as Day 0) to hospital discharge (or 7 days post-procedure, whichever earlier). The name, duration of treatment, reasons for treatment, route of administration, and dosage of the used anticoagulants/antiplatelet drugs and antibiotics should be entered in eCRF. However, the data on antibiotics will not be collected for the continued access registry.

#### 8.6.2 Blood purification

Concerning periprocedural blood purification therapy, for dialysis given from immediately before the study procedure through to post-procedure hospital discharge (day of discharge or 7 days post-procedure, whichever earlier), the date of therapy, type of dialysis, dialysis condition, and anticoagulant used at dialysis should be entered in eCRF. Also at 1 year post-procedure, similarly to the periprocedural period, dialysis data should be collected to check the dialysis status.

#### 8.6.3 Other concomitant drug/therapy

After the start of study procedure, the data on other drugs and therapies concomitantly used in the treatment of an AE and complication that can be a risk factor will be collected until 1 year post-procedure. Of the concomitant drugs, only for the cardiovascular agents applicable to the following therapeutic category, the name, duration of administration, reason for use, route of administration, and dosage should be entered in eCRFs, and for the concomitant therapies, the name, duration of concomitant use, and reason for concomitant use should be entered in eCRFs. However, for Continued Access Registry, these data may be collected as much as possible.

<Concomitant cardiovascular drugs for which data will be collected>
- Inotropic agent
- Antiarrhythmic agent
- Diuretic
- Hypotensive agent
  - Angiotensin-converting enzyme inhibitor (ACE-I)
  - Angiotensin II receptor blocker (ARB)
  - Renin inhibitor
  - β-blocker
  - α-blocker
  - α-β-blocker
  - Calcium-channel blocker (CCB)
  - Aldosterone receptor antagonist
- Capillary stabilizer





- Vasoconstrictor
- Vasodilator
  - Coronary vasodilator
  - Peripheral vasodilator
- Hyperlipidemia agent
  - HMG-CoA reductase inhibitor (statin)

# 9 STUDY ENDPOINTS

## 9.1 Primary Endpoints

- Mortality at 1 year post-procedure

<Rationales for the setting>

Based on the fact that the study device EWJ-003 is clinically positioned as a device that enables us to treat chronic dialysis AS patients who have not been eligible for sAVR and have not had any radical treatments so far, it is important to evaluate whether or not improvement in the prognosis, the goal of the therapy, could be achieved for evaluation of the safety and efficacy of EWJ-003. Since the Valve Academic Research Consortium (VARC) guidelines recommend that the morality at 1 year post-procedure be set for the primary endpoint in clinical trials,[55] the mortality at 1 year post-procedure was set up for the primary endpoint for this clinical trial.

## 9.2 Secondary Endpoints

### 9.2.1 Secondary safety endpoints

- Composite endpoint: Post-procedure 30 days, 6 months, 1 year, and 2 to 5 years annually
  - Death and stroke

- Single endpoints: Post-procedure 30 days, 6 months, 1 year, and 2 to 5 years annually
  - Death (cardiovascular, non-cardiovascular)
  - MI (periprocedural, spontaneous)
  - Stroke (disabling, non-disabling)
  - Bleeding (life-threatening or disabling, severe, mild)
  - Vascular access site/access-related complications
  - Severe vascular complications
  - Conduction disorder/arrhythmia
  - Conduction disorder requiring new pacemaker implantation
  - Aortic valve re-intervention
  - Coronary obstruction
  - Endocarditis
  - Valve explants
  - Structural valve deterioration
  - Nonstructural valve dysfunction





### 9.2.2 Secondary efficacy endpoints

- Device success: 30 days after procedure
- Length of post-procedural hospitalization/ICU stay: At discharge
- NYHA classification: Post-procedure 30 days, 6 months, 1 year, and 2 to 5 years annually
- Six-minute walk test: Post-procedure 30 days and 1 year
- Quality of life (QOL) (EuroQOL, short form 12-item health survey [SF-12]): Post-procedure 30 days, 6 months, 1 year, and 2 to 5 years annually

### 9.2.3 Secondary valve performance endpoints

- Echocardiography: Post-procedure 30 days, 6 months, 1 year, and 2 to 5 years annually
  - Mean pressure gradient
  - Peak gradient
  - EOA
  - EOAi
  - Aortic valve regurgitation (paravalvular, transvalvular)
  - LVEF
  - Left ventricular mass
  - Left ventricular mass index (LVMI)

# 10 TEST/OBSERVATION DATA COLLECTION

## 10.1 Test/Observation Schedule

All registered subjects in this clinical trial will receive the tests/observations shown in Section 10.2 “Test/observation items”. Post-procedural follow-up observation will be performed at post-procedure 30 days, 6 months, 1 year, and 2 to 5 years annually.

The permissible time window for each test/observation period is as shown in Table 10-1 and Table 10-2, and the day of procedure is counted as Day 0. The time of the day of procedure is specified as between 0:00 and 23:59, and 24:00 should be expressed as 0:00. If the procedure spans before and after 0:00, the day when the procedure was started should be counted as date of procedure (initial day). The time of the start and end of the procedure is the time when invasion such as incision was made on the access site and the time when closing the access site such as incision site was completed, respectively.

The test/observation schedule is shown in Table 10-3. The test/observation schedule for the continued access registry is as shown in Table 10-4.





Table 10-1: Permissible time windows for the tests/observations

<up to 6 months post-procedure>

| Test/observation timing | Baseline [a] | Procedure [b] | Immediately after procedure | Post-procedural follow-up observation | | |
|---|---|---|---|---|---|---|
| | | | | Hospital discharge | 30 days post-procedure | 6 months post-procedure |
| Reference date (time) | - | Day 0 | Up to 72 hours after exiting the operation room | 7 days post-procedure or hospital discharge, whichever comes earlier | 30 days post-procedure | 182 days post-procedure |
| Permissible time window | Within 60 days pre-procedure | - | - | ± 2 days | -7 days/+14 days | ± 30 days |

a) The 12-lead ECG should be performed within 48 hours prior to entering the operation room, clinical laboratory tests within 14 days prior to the procedure, and coronary angiography and aortofemoral blood vessel evaluation (CT, MRI, or X-ray) within 90 days pre-procedure (see Section 10.2.1 “Baseline”). For the continued access registry, except cases that may be clinically valid, coronary angiography should be performed within 1 year prior to the study procedure.

b) Cardiac catheter test at procedure should be performed immediately before and after the procedure.

Table 10-2: Permissible time windows for the tests/observations

<at 1 year post-procedure and thereafter>

| Test/observation timing | Post-procedural follow-up observation | | | | |
|---|---|---|---|---|---|
| | 1 year post-procedure | 2 years post-procedure | 3 years post-procedure | 4 years post-procedure | 5 years post-procedure |
| Reference date | 365 days post-procedure | 730 days post-procedure | 1095 days post-procedure | 1460 days post-procedure | 1825 days post-procedure |
| Permissible time window | ± 30 days | ± 45 days | ± 45 days | ± 45 days | ± 45 days |





Table 10-3: Schedule of Tests and Observations

| Tests/observations \ Timing | Baseline (Within 60 days pre-procedure) | During procedure | Immediately after procedure (Within 72 hours post-procedure) | Discharge or 7 days post-procedure (± 2 days) | 30 days post-procedure (-7 days, +14 days) | 6 months post-procedure (± 30 days) | 1 year post-procedure (± 30 days) | 2 - 5 years post-procedure (± 45 days) | Discontinued | Unscheduled visit |
|---|---|---|---|---|---|---|---|---|---|---|
| Informed consent | X | | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | | |
| Patient background | X | | | | | | | | | |
| Surgical risk assessment*1 | X | | | | | | | | | |
| NYHA classification of cardiac performance | X | | | X | X | X | X | X | | |
| CCS status of stable angina | X | | | X | X | X | X | X | | |
| Neurological assessment*2 (NIHSS, mRS) | X | | | | X | X | X | | | |
| Blood pressure | X | | | X | X | X | X | | | |
| 12-lead ECG | X*3 | | X | X | X | X | X | | | |
| Chest X-ray | X | | X | X | X | X | X | | | |
| Head CT | X | | | | X | X | X | | | |
| 6-minute walk test | X | | | | X | | X | | | |
| Clinical laboratory test: Hematology | X*4 | | | | X | X | X | | | |
| Clinical laboratory test: Biochemistry | X*4 | | | | X | X | X | | | |
| Clinical laboratory test: Coagulation | X*4 | | | | X | X | X | | | |
| Clinical laboratory test: Cardiac enzyme | X*4 | | X | X | X | X | X | | | |
| Echocardiography | X | X*8 | | X*11 | X*11 | X*11 | X*11 | X*11 | | |
| Cardiac CT | X | | | | | | | | | |
| Coronary angiography | X*5 | | | | | | | | | |
| Aortofemoral imaging | X*6 | | | | | | | | | |
| Cardiac catheterization | | X*9 | | | | | | | | |
| QOL questionnaire (EuroQOL,SF-12) | X | | | | X | X | X | X | | |
| Procedure information | | X | | | | | | | | |
| Anticoagulant/antiplatelet drugs | X*7 | ← | ― | ― | ― | X | → | | | |
| Antibiotic | X*7 | ← | X | → | | | | | | |
| Blood purification | ← | X*10 | → | | | | X | | | |
| Other concomitant medication/therapy | | ← | ― | X | ― | → | | X*12 | X*12 | |
| Adverse event/device deficiency | | ← | ― | ― | ― | X | ― | → | | |

*1 Calculate STS score, Logistic EuroSCORE, and EuroSCORE II.
*2 For patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.
*3 Perform within 48 hours prior to entering the operating room.
*4 Perform within 14 days prior to the study procedure.
*5 Perform within 90 days prior to the study procedure.
*6 Perform CT, MRI, or X-ray within 90 days prior to the study procedure.
*7 Start assessment from 7 days pre-procedure.
*8 Measure the aortic annulus diameter, and perform observation items of cardiac catheterization according to the situation.
*9 Perform pre- and post-study procedure. May be performed by echocardiography according to the situation.
*10 Assess dialysis information performed from the latest date prior to the study procedure to discharge (at discharge date or 7 days post-procedure, whichever came earlier).
*11 Baseline BSA value must be used for calculation of EOAi and LVMI.
*12 Assess other concomitant medication/therapy, excluding anticoagulation/antiplatelet, antibiotic, and hemodialysis, within 1 year post-procedure.

Table 10-4: Schedule of Tests and Observations for Continued Access Registry

| Tests/Observations \ Timing | | Baseline (Within 60 days pre-procedure) | During procedure | Immediately after procedure (Within 72 hours pre-procedure) | Discharge or 7 days post-procedure (± 4 days) | 30 days post-procedure (– 7 days, + 14 days) | 6 months post-procedure (± 30 days) | 1 year post-procedure (± 30 days) | 2 - 5 years post-procedure (± 45 days) | Discontinued | Unscheduled visit |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed consent | | X | | | | | | | | | |
| Inclusion/exclusion criteria for continued access registry | | X | | | | | | | | | |
| Patient background | | X | | | | | | | | | |
| Surgical risk assessment*1 | | X | | | | | | | | | |
| NYHA classification of cardiac performance | | X | | | X | X | X | X | X | | |
| CCS status of stable angina | | X | | | X | X | X | X | X | | |
| Neurological assessment*2 (NIHSS, mRS) | | X | | | | X | X*3 | X*3 | | | |
| Blood pressure | | X | | | X | X | X | X | | | |
| 12-lead ECG | | X*4 | | X | X | X | X | X | | | |
| Chest X-ray | | X | | X | X | X | X | X | | | |
| Head CT | | X | | | | X | X*3 | X*3 | | | |
| Clinical laboratory test | Hematology | X*5 | | | | X | X | X | | | |
| | Biochemistry | X*5 | | | | X | X | X | | | |
| | Coagulation | X*5 | | | | X | X | X | | | |
| | Cardiac enzyme | X*5 | | X | X | X | X | X | | | |
| Echocardiography | | X | X*9 | | X*12 | X*12 | X*12 | X*12 | X*12 | | |
| Cardiac CT | | X | | | | | | | | | |
| Coronary angiography | | X*6 | | | | | | | | | |
| Aortofemoral imaging | | X*7 | | | | | | | | | |
| Cardiac catheterization | | | X*10 | | | | | | | | |
| QOL questionnaire (EuroQOL_SF-12) | | X | | | | X*13 | X*13 | X*13 | X*13 | | |
| Procedure information | | | X | | | | | | | | |
| Anticoagulant/antiplatelet drugs | | X*8 | ← | ← | ← | ← | X | → | → | → | → |
| Blood purification | | ← | X*11 → | | | | | X | | | |
| Other concomitant medication/therapy | | | ← | ← | ← | X*14 | → | → | | X*14 | X*14 |
| Adverse event/device deficiency | | | ← | ← | ← | ← | X | → | → | → | → |

*1 Calculate STS score, Logistic EuroSCORE, and EuroSCORE II.
*2 For patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.
*3 Subjects who developed stroke only.
*4 Perform within 48 hours prior to entering the operating room.
*5 Perform within 14 days prior to the study procedure.
*6 Except cases that may be clinically valid, perform within 1 year prior to the study procedure.
*7 Perform CT, MRI, or X-ray within 90 days prior to the study procedure.
*8 Start assessment from 7 days pre-procedure.
*9 Measure the aortic annulus diameter, and perform observation items of cardiac catheterization according to the situation.
*10 Perform pre- and post-study procedure. May be performed by echocardiography according to the situation.
*11 Assess dialysis information performed from the latest date prior to the study procedure to discharge (at discharge date or 7 days post-procedure, whichever came earlier).
*12 Baseline BSA value must be used for calculation of EOAi and LVMI.
*13 Subjects who were included in the continued access registry under Protocol ver. 5 will require no post-procedural QOL questionnaire.
*14 Where possible, assess other concomitant medication/therapy, excluding anticoagulation/antiplatelet, antibiotic, and hemodialysis, within 1 year post-procedure.





## 10.2 Tests/Observations

### 10.2.1 Baseline

For the baseline tests/observations, the following data will be collected from subject consent to before the study procedure. From the standpoint of protection of subjects, if any data are available on the tests performed within the permissible time windows specified in the protocol, the data obtained before informed consent and data used for screening may be used as baseline data.

- Informed consent
- Conformance to the inclusion/exclusion criteria
- Patient background
  - Demographic background
    Sex, date of birth, and age (calculated from the date of birth)
  - Physical finding
    Height, weight, body surface area (BSA), and BMI
    * BSA and BMI will be calculated from height and weight in the following formulas.
      - BSA = $0.007184 \times \text{Weight [kg]}^{0.425} \times \text{Height [cm]}^{0.725}$
      - BMI = $\text{Weight [kg]}/\text{Height [m]}^2$
  - Clinical background
    Primary disease, risk factors (pre-procedural complication, past history, history of syncope not associated with atrioventricular block, number of hospitalization for AS in the past 6 months, and stroke in the past 12 months), type of dialysis (hemodialysis or peritoneal dialysis), the starting time of dialysis, duration of dialysis (to be calculated from the starting time of dialysis), and primary disease for introduction of dialysis
- Surgical risk assessment
  After investigation/evaluation of surgical risks and risk score, evaluate patients who are not eligible for safe open surgical therapy as to whether or not the best therapy is treatment with EWJ-003.
  - STS score [http://riskcalc.sts.org/stswebriskcalc/#/]
  - Logistic EuroSCORE [http://www.euroscore.org/calcold.html]
  - EuroSCORE II [http://www.euroscore.org/calc.html]
  * The results of risk score should be printed out and affixed to medical records, etc.
- NYHA classification of cardiac performance (see Section 30 “GLOSSARY”)
- Canadian Cardiovascular Society (CCS) status of stable angina (see Section 30 “GLOSSARY”)
- Neurological examination
  - National Institutes of Health Stroke Scale (NIHSS) (see Appendix 1)
  - Modified Rankin Scale (mRS) (see Appendix 2)
  * Neurological assessment should be performed by a neurologist, neurosurgeon, or a physician





who is able to perform appropriate assessment.

- Blood pressure (systolic, diastolic)
- 12-lead ECG (to be performed within 48 hours prior to entering the operating room)
- Chest X-ray
- Head CT
- Six Minute Walk Test (see Appendix 3)
- Laboratory tests (to be performed within 14 days pre-procedure)
  - Hematology
    Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophil, lymphocyte, monocyte, eosinophil, basophil)
  - Biochemistry
    Sodium, potassium, creatinine, urea nitrogen, albumin, total bilirubin, CRP, GOT(AST), GPT(ALT), LDH, hemoglobin A1c, glycated albumin, phosphate, calcium
  - Coagulation
    Prothrombin time, activated partial thromboplastin time
  - Cardiac enzyme
    CK and troponin, or CK-MB and troponin
- Echocardiography
  Perform echocardiography in reference to the Echo Core Laboratory Procedure to measure/evaluate the following items. The resulted echocardiographic images should be submitted to the Echo Core Laboratory.
  [Measurements/endpoints]
  Cardiac output, aortic valve pressure gradient (mean/maximum), AVA, AVA index, aortic valve regurgitation (severity/regurgitation site), aortic annulus diameter*, maximum aortic flow velocity, LVEF, left ventricular mass, LVMI, valvular and paravalvular conditions
  * The aortic annulus diameter should be estimated from the left ventricular outflow tract (LVOT) dimension.
- Cardiac CT
  [Measurements/endpoints]
  Aortic annulus diameter, aortic annulus area, distance from aortic annulus to coronary ostium
- Coronary angiography (to be performed within 90 days pre-procedure)
  * If a subject has no hypersensitivity to contrast media, but contrast media cannot be used due to other disease, MRI may be used.
- Aortofemoral vascular evaluation (to be performed within 90 days pre-procedure)
  Perform CT, MRI, or X-ray to evaluate from the aorta through to the femoral artery.
- QOL questionnaire
  - EuroQOL (see Appendix 4)





  - SF-12 (Appendix 5)
- Anticoagulant/antiplatelet drugs (to be investigated from 7 days prior to the procedure)
- Antibiotics (to be investigated from 7 days prior to the procedure)
- Blood purification
  Investigate the latest dialysis prior to the procedure.

### 10.2.2 During procedure

The test/observation during procedure will collect the data on the following items.

- Echocardiography (perform observation items of cardiac catheter test according to the aortic annulus diameter and situation)
- Cardiac catheter test (to be performed immediately before and after the procedure. It may be replaced with echocardiography according to the situation)
  [Measurements/endpoints]
  Aortic pressure (systolic/diastolic/mean), aortic valve pressure gradient (mean/maximum), AVA (immediately before procedure only), EOA (immediately after procedure only), aortic valve regurgitation (severity/regurgitation site)
- Procedure information
  Date of procedure, delivery means, time of procedure, predilatation information, valve implantation information, maximum ACT, anesthesia procedure, X-ray status, contrast media status, evaluation of procedure, device information, aortic annulus diameter used for selection of THV size and measurement method
- Anticoagulant/antiplatelet drugs
- Antibiotic
- Other concomitant drugs/therapies (to be investigated from right after the start of the study procedure)
- AE/defect (to be investigated from right after the start of the study procedure)
  For a patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.

### 10.2.3 Immediately after procedure

The test/observation immediately after the procedure will collect the data on the following items until 72 hours after exiting the operation room.

- 12-lead ECG
- Chest X-ray

- Cardiac enzyme test (CK and troponin, or CK-MB and troponin)
- Anticoagulant/antiplatelet drugs
- Antibiotic
- Blood purification
- Other concomitant medication/therapy
- AE/device deficiency
  For a patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.

### 10.2.4 Hospital discharge

The tests/observation at hospital discharge will collect the data on the following items on the day of discharge or 7 days post-procedure, whichever comes earlier (± 2 days).

- NYHA classification of cardiac performance (see Section 30 "GLOSSARY")
- CCS status of stable angina (see Section 30 "GLOSSARY")
- Blood pressure (systolic, diastolic)
- 12-lead ECG
- Chest X-ray
- Cardiac enzyme test (CK and troponin, or CK-MB and troponin)
- Echocardiography
  Perform echocardiography in reference to the Echo Core Laboratory Procedure to measure/evaluate the following items.
  [Measurements/endpoints]
  Cardiac output, aortic valve pressure gradient (mean/maximum), EOA, EOAi*, aortic valve regurgitation (severity/regurgitation site), maximum blood flow rate, LVEF, left ventricular mass, LVMI*
  * Baseline BSA values must be used for calculation of EOAi and LVMI.
- Anticoagulant/antiplatelet drugs
- Antibiotic
- Blood purification
- Other concomitant medication/therapy
- AE/device deficiency
  For a patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.





### 10.2.5 At 30 days post-procedural follow-up observation

The tests/observation at 30 days post-procedure should be performed at 30 days post-procedural visit (-7 days, +14 days) to collect the data on the following items.

- NYHA classification of cardiac performance (see Section 30 "GLOSSARY")
- CCS status of stable angina (see Section 30 "GLOSSARY")
- Neurological examination
  - NIHSS (see Appendix 1)
  - mRS (see Appendix 2)
  * Neurological assessment should be performed by a neurologist, neurosurgeon, or a physician who is able to perform appropriate assessment.
- Blood pressure (systolic, diastolic)
- 12-lead ECG
- Chest X-ray
- Head CT
- Six-minute walk test (see Appendix 3)
- Clinical laboratory test
  - Hematology
    Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophil, lymphocyte, monocyte, eosinophil, basophil)
  - Biochemistry
    Sodium, potassium, creatinine, urea nitrogen, albumin, total bilirubin, CRP, GOT(AST), GPT(ALT), LDH, hemoglobin A1c, glycated albumin, phosphate, calcium
  - Coagulation
    Prothrombin time, activated partial thromboplastin time
  - Cardiac enzyme
    CK and troponin, or CK-MB and troponin
- Echocardiography
  Perform echocardiography in reference to the Echo Core Laboratory Procedure to measure/evaluate the following items. The resulted echocardiographic images should be submitted to the Echo Core Laboratory.
  [Measurements/endpoints]
  Cardiac output, aortic valve pressure gradient (mean/maximum), EOA, EOAi*, aortic valve regurgitation (severity/regurgitation site), maximum blood flow rate, LVEF, left ventricular mass, LVMI*
  * Baseline BSA values must be used for calculation of EOAi and LVMI.





- QOL questionnaire
  - EuroQOL (see Appendix 4)
  - SF-12 (Appendix 5)
- Anticoagulant/antiplatelet drugs
- Other concomitant medication/therapy
- AE/device deficiency
  For a patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.

### 10.2.6 At 6 months post-procedural follow-up

The tests/observation at 6 months post-procedural follow-up should be performed at 182 days post-procedural visit (± 30 days) to collect the data on the following items.

- NYHA classification of cardiac performance (see Section 30 "GLOSSARY")
- CCS status of stable angina (see Section 30 "GLOSSARY")
- Neurological examination
  - NIHSS (see Appendix 1)
  - mRS (see Appendix 2)
  * Neurological assessment should be performed by a neurologist, neurosurgeon, or a physician who is able to perform appropriate assessment.
- Blood pressure (systolic, diastolic)
- 12-lead ECG
- Chest X-ray
- Head CT
- Clinical laboratory test
  - Hematology
    Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophil, lymphocyte, monocyte, eosinophil, basophil)
  - Biochemistry
    Sodium, potassium, creatinine, urea nitrogen, albumin, total bilirubin, CRP, GOT(AST), GPT(ALT), LDH, hemoglobin A1c, glycated albumin, phosphate, calcium
  - Coagulation
    Prothrombin time, activated partial thromboplastin time
  - Cardiac enzyme
    CK and troponin, or CK-MB and troponin
- Echocardiography





  Perform echocardiography in reference to the Echo Core Laboratory Procedure to measure/evaluate the following items. The resulted echocardiographic images should be submitted to the Echo Core Laboratory.
  [Measurements/endpoints]
  Cardiac output, aortic valve pressure gradient (mean/maximum), EOA, EOAi*, aortic valve regurgitation (severity/regurgitation site), maximum blood flow rate, LVEF, left ventricular mass, LVMI*
  * Baseline BSA values must be used for calculation of EOAi and LVMI.
- QOL questionnaire
  - EuroQOL (see Appendix 4)
  - SF-12 (Appendix 5)
- Anticoagulant/antiplatelet drugs
- Other concomitant medication/therapy
- AE/device deficiency
  For a patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.

### 10.2.7 At 1 year post-procedural follow-up observation

The tests/observation at 1 year post-procedural follow-up should be performed at 365 days post-procedural visit (± 30 days) to collect the data on the following items.

- NYHA classification of cardiac performance (see Section 30 "GLOSSARY")
- CCS status of stable angina (see Section 30 "GLOSSARY")
- Neurological examination
  - NIHSS (see Appendix 1)
  - mRS (see Appendix 2)
  * Neurological assessment should be performed by a neurologist, neurosurgeon, or a physician who is able to perform appropriate assessment.
- Blood pressure (systolic, diastolic)
- 12-lead ECG
- Chest X-ray
- Head CT
- Six-minute walk test (see Appendix 3)
- Clinical laboratory test
  - Hematology
    Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophil, lymphocyte, monocyte, eosinophil,

basophil)
  - Biochemistry
    Sodium, potassium, creatinine, urea nitrogen, albumin, total bilirubin, CRP, GOT(AST), GPT(ALT), LDH, hemoglobin A1c, glycated albumin, phosphate, calcium
  - Coagulation
    Prothrombin time, activated partial thromboplastin time
  - Cardiac enzyme
    CK and troponin, or CK-MB and troponin
- Echocardiography
  Perform echocardiography in reference to the Echo Core Laboratory Procedure to measure/evaluate the following items. The resulted echocardiographic images should be submitted to the Echo Core Laboratory.
  [Measurements/endpoints]
  Cardiac output, aortic valve pressure gradient (mean/maximum), EOA, EOAi*, aortic valve regurgitation (severity/regurgitation site), maximum blood flow rate, LVEF, left ventricular mass, LVMI*
  * Baseline BSA values must be used for calculation of EOAi and LVMI.
- QOL questionnaire
  - EuroQOL (see Appendix 4)
  - SF-12 (Appendix 5)
- Anticoagulant/antiplatelet drugs
- Blood purification
  Investigate the latest dialysis prior to the 1 year post-procedural follow-up visit.
- Other concomitant medication/therapy
- AE/device deficiency
  For a patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.

### 10.2.8 Years 2 through 5 annual post-procedure visits

The tests/observation at 2 to 5 years post-procedural follow-up should be performed within the permissible time windows shown in Section 10.1 "Test/observation schedule" to collect the data on the following items.

- NYHA classification of cardiac performance (see Section 30 "GLOSSARY")
- CCS status of stable angina (see Section 30 "GLOSSARY")
- Echocardiography
  Perform echocardiography in reference to the Echo Core Laboratory Procedure to measure/evaluate the following items. The resulted echocardiographic images should be





submitted to the Echo Core Laboratory.
  [Measurements/endpoints]
  Cardiac output, aortic valve pressure gradient (mean/maximum), EOA, EOAi*, aortic valve regurgitation (severity/regurgitation site), maximum blood flow rate, LVEF, left ventricular mass, LVMI*
  * Baseline values must be used for calculation of EOAi and LVMI.
- QOL questionnaire
  - EuroQOL (see Appendix 4)
  - SF-12 (Appendix 5)
- Anticoagulant/antiplatelet drugs
- AE/device deficiency

### 10.2.9 At trial discontinuation

At trial discontinuation, collect the data on the following items. If any AE is found at discontinuation, a follow-up investigation should be performed, and also the safety after discontinuation should be followed up as much as possible. For detailed subject's trial discontinuation, see Sections 14.1 and 14.2.

- Anticoagulant/antiplatelet drugs
- Other concomitant drugs/therapies (until 1 year post-procedure)
- AE/device deficiency
  For a patient who has suffered a stroke within 1 year post-procedure, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.

### 10.2.10 Unscheduled visit

If a subject made an unscheduled visit other than those specified in the protocol formedical necessity, collect the data on the following items.

- Anticoagulant/antiplatelet drugs
- Other concomitant drugs/therapies (until 1 year post-procedure)
- AE/device deficiency
  For a patient who has suffered a stroke within 1 year post-procedure, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.





## 10.3 Test/Observation Items for the Continued Access Registry

### 10.3.1 Baseline

For the baseline tests/observations, the following data will be collected from subject consent to before the study procedure. From the standpoint of protection of subjects, if any data are available on the tests performed within the permissible time windows specified in the protocol, the data obtained before informed consent and data used for screening may be used as baseline data.

- Informed consent
- Conformance to the inclusion/exclusion criteria for the continued access registry
- Patient background
  - Demographic background
    Sex, date of birth, and age (calculated from the date of birth)
  - Physical finding
    Height, weight, BSA, and BMI
    * BSA and BMI will be calculated from height and weight in the following formulas.
      - BSA = 0.007184 × Weight [kg]$^{0.425}$ × Height [cm]$^{0.725}$
      - BMI = Weight [kg]/Height [m]$^2$
  - Clinical background
    Primary disease, risk factors (pre-procedural complication, past history, history of syncope not associated with atrioventricular block, number of hospitalization for AS in the past 6 months, and stroke in the past 12 months), type of dialysis (hemodialysis or peritoneal dialysis), the starting time of dialysis, duration of dialysis (to be calculated from the starting time of dialysis), and primary disease for introduction of dialysis
- Surgical risk assessment
  After investigation/evaluation of surgical risks and risk score, evaluate patients who are not eligible for safe open surgical therapy as to whether or not the best therapy is treatment with EWJ-003.
  - STS score [http://riskcalc.sts.org/stswebriskcalc/#/]
  - Logistic EuroSCORE [http://www.euroscore.org/calcold.html]
  - EuroSCORE II [http://www.euroscore.org/calc.html]
  * The results of risk score should be printed out and affixed to medical records, etc.
- NYHA classification of cardiac performance (see Section 30 "GLOSSARY")
- CCS status of stable angina (see Section 30 "GLOSSARY")
- Neurological examination
  - NIHSS (see Appendix 1)
  - mRS (see Appendix 2)
  * Neurological assessment should be performed by a neurologist, neurosurgeon, or a physician





who is able to perform appropriate assessment.
- Blood pressure (systolic, diastolic)
- 12-lead ECG (to be performed within 48 hours prior to entering the operating room)
- Chest X-ray
- Head CT
- Laboratory tests (to be performed within 14 days pre-procedure)
  - Hematology
    Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophil, lymphocyte, monocyte, eosinophil, basophil)
  - Biochemistry
    Sodium, potassium, creatinine, urea nitrogen, albumin, total bilirubin, CRP, GOT(AST), GPT(ALT), LDH, hemoglobin A1c, glycated albumin, phosphate, calcium
  - Coagulation
    Prothrombin time, activated partial thromboplastin time
  - Cardiac enzyme
    CK and troponin, or CK-MB and troponin
- Echocardiography
  Perform echocardiography in reference to the Echo Core Laboratory Procedure to measure/evaluate the following items. The resulted echocardiographic images should be submitted to the Echo Core Laboratory.
  [Measurements/endpoints]
  Cardiac output, aortic valve pressure gradient (mean/maximum), AVA, AVA index, aortic valve regurgitation (severity/regurgitation site), aortic annulus diameter*, maximum aortic flow velocity, LVEF, left ventricular mass, LVMI, valvular and paravalvular conditions
  * The aortic annulus diameter should be estimated from the LVOT dimension.
- Cardiac CT
  [Measurements/endpoints]
  Aortic annulus diameter, aortic annulus area, distance from aortic annulus to coronary ostium
- Coronary angiography (except cases that may be clinically valid, perform within 1 year prior to the study procedure)
  * If a subject has no hypersensitivity to contrast media, but contrast media cannot be used due to other disease, MRI may be used.
- Aortofemoral vascular evaluation (to be performed within 90 days pre-procedure)
  Perform CT, MRI, or X-ray to evaluate from the aorta through to the femoral artery.
- QOL questionnaire
  - EuroQOL (see Appendix 4)
  - SF-12 (Appendix 5)

- Anticoagulant/antiplatelet drugs (investigated from 7 days prior to the procedure)
- Blood purification
  Investigate the latest dialysis prior to the procedure.

### 10.3.2 During procedure

The test/observation during procedure will collect the data on the following items.

- Echocardiography (perform observation items of cardiac catheter test according to the aortic annulus diameter and situation)
- Cardiac catheter test (to be performed immediately before and after the procedure. It may be replaced with echocardiography according to the situation)
  [Measurements/endpoints]
  Aortic pressure (systolic/diastolic/mean), aortic valve pressure gradient (mean/maximum), AVA (immediately before procedure only), EOA (immediately after procedure only), aortic valve regurgitation (severity/regurgitation site)
- Procedure information
  Date of procedure, delivery means, time of procedure, predilatation information, valve implantation information, maximum ACT, anesthesia procedure, X-ray status, contrast media status, evaluation of procedure, device information, aortic annulus diameter used for selection of THV size and measurement method
- Anticoagulant/antiplatelet drugs
- Other concomitant drugs/therapies (to be investigated from right after the start of the study procedure)
- AE/defect (to be investigated from right after the start of the study procedure)
  For a patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.

### 10.3.3 Immediately after procedure

The test/observation immediately after the procedure will collect the data on the following items until 72 hours after exiting the operation room.

- 12-lead ECG
- Chest X-ray
- Cardiac enzyme test (CK and troponin, or CK-MB and troponin)
- Anticoagulant/antiplatelet drugs
- Blood purification





- Other concomitant medication/therapy
- AE/device deficiency
  For a patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.

### 10.3.4 Hospital discharge

For the tests/observation at hospital discharge will collect the data on the following items on the day of discharge or 7 days post-procedure, whichever comes earlier (± 2 days).

- NYHA classification of cardiac performance (see Section 30 “GLOSSARY”)
- CCS status of stable angina (see Section 30 “GLOSSARY”)
- Blood pressure (systolic, diastolic)
- 12-lead ECG
- Chest X-ray
- Cardiac enzyme test (CK and troponin, or CK-MB and troponin)
- Echocardiography
  Perform echocardiography in reference to the Echo Core Laboratory Procedure to measure/evaluate the following items.
  [Measurements/endpoints]
  Cardiac output, aortic valve pressure gradient (mean/maximum), EOA, EOAi*, aortic valve regurgitation (severity/regurgitation site), maximum blood flow rate, LVEF, left ventricular mass, LVMI*
  * Baseline BSA values must be used for calculation of EOAi and LVMI.
- Anticoagulant/antiplatelet drugs
- Blood purification
- Other concomitant medication/therapy
- AE/device deficiency
  For a patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.

### 10.3.5 At 30 days post-procedural follow-up observation

The tests/observation at 30 days post-procedure should be performed at 30 days post-procedural visit (-7 days, +14 days) to collect the data on the following items.

- NYHA classification of cardiac performance (see Section 30 “GLOSSARY”)
- CCS status of stable angina (see Section 30 “GLOSSARY”)





- Neurological examination
  - NIHSS (see Appendix 1)
  - mRS (see Appendix 2)
  * Neurological assessment should be performed by a neurologist, neurosurgeon, or a physician who is able to perform appropriate assessment.
- Blood pressure (systolic, diastolic)
- 12-lead ECG
- Chest X-ray
- Head CT
- Clinical laboratory test
  - Hematology
    Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophil, lymphocyte, monocyte, eosinophil, basophil)
  - Biochemistry
    Sodium, potassium, creatinine, urea nitrogen, albumin, total bilirubin, CRP, GOT(AST), GPT(ALT), LDH, hemoglobin A1c, glycated albumin, phosphate, calcium
  - Coagulation
    Prothrombin time, activated partial thromboplastin time
  - Cardiac enzyme
    CK and troponin, or CK-MB and troponin
- Echocardiography
  Perform echocardiography in reference to the Echo Core Laboratory Procedure to measure/evaluate the following items. The resulted echocardiographic images should be submitted to the Echo Core Laboratory.





  [Measurements/endpoints]
  Cardiac output, aortic valve pressure gradient (mean/maximum), EOA, EOAi*, aortic valve regurgitation (severity/regurgitation site), maximum blood flow rate, LVEF, left ventricular mass, LVMI*
  * Baseline BSA values must be used for calculation of EOAi and LVMI.
- QOL questionnaire
  - EuroQOL (see Appendix 4)
  - SF-12 (Appendix 5)
- Anticoagulant/Antiplatelet drugs
- Other concomitant medication/therapy
- AE/device deficiency
  For a patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.

### 10.3.6 At 6 months post-procedural follow-up

The tests/observation at 6 months post-procedural follow-up should be performed at 182 days post-procedural visit (± 30 days) to collect the data on the following items.

- NYHA classification of cardiac performance (see Section 30 “GLOSSARY”)
- CCS status of stable angina (see Section 30 “GLOSSARY”)
- Neurological examination (to be performed only for patients diagnosed with a stroke after the procedure)
  - NIHSS (see Appendix 1)
  - mRS (see Appendix 2)
  * Neurological assessment should be performed by a neurologist, neurosurgeon, or a physician who is able to perform appropriate assessment.
- Blood pressure (systolic, diastolic)
- 12-lead ECG
- Chest X-ray
- Head CT (to be performed only for patients diagnosed with a stroke after the procedure)
- Clinical laboratory test
  - Hematology
    Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophil, lymphocyte, monocyte, eosinophil, basophil)
  - Biochemistry
    Sodium, potassium, creatinine, urea nitrogen, albumin, total bilirubin, CRP, GOT(AST),

GPT(ALT), LDH, hemoglobin A1c, glycated albumin, phosphate, calcium
- ○ Coagulation
  Prothrombin time, activated partial thromboplastin time
- ○ Cardiac enzyme
  CK and troponin, or CK-MB and troponin

- Echocardiography
  Perform echocardiography in reference to the Echo Core Laboratory Procedure to measure/evaluate the following items. The resulted echocardiographic images should be submitted to the Echo Core Laboratory.
  [Measurements/endpoints]
  Cardiac output, aortic valve pressure gradient (mean/maximum), EOA, EOAi*, aortic valve regurgitation (severity/regurgitation site), maximum blood flow rate, LVEF, left ventricular mass, LVMI*
  * Baseline BSA values must be used for calculation of EOAi and LVMI.
- QOL questionnaire
  - ○ EuroQOL (see Appendix 4)
  - ○ SF-12 (Appendix 5)
- Anticoagulant/antiplatelet drugs
- Other concomitant medication/therapy
- AE/device deficiency
  For a patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.

### 10.3.7 At 1 year post-procedural follow-up observation

The tests/observation at 1 year post-procedural follow-up should be performed at 365 days post-procedural visit (± 30 days) to collect the data on the following items.

- NYHA classification of cardiac performance (see Section 30 “GLOSSARY”)
- CCS status of stable angina (see Section 30 “GLOSSARY”)
- Neurological examination (to be performed only for patients diagnosed with a stroke after the procedure)
  - ○ NIHSS (see Appendix 1)
  - ○ mRS (see Appendix 2)
  - * Neurological assessment should be performed by a neurologist, neurosurgeon, or a physician who is able to perform appropriate assessment.
- Blood pressure (systolic, diastolic)
- 12-lead ECG





- Chest X-ray
- Head CT (to be performed only for patients diagnosed with a stroke after the procedure)
- Clinical laboratory test
  - ○ Hematology
    Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophil, lymphocyte, monocyte, eosinophil, basophil)
  - ○ Biochemistry
    Sodium, potassium, creatinine, urea nitrogen, albumin, total bilirubin, CRP, GOT(AST), GPT(ALT), LDH, hemoglobin A1c, glycated albumin, phosphate, calcium
  - ○ Coagulation
    Prothrombin time, activated partial thromboplastin time
  - ○ Cardiac enzyme
    CK and troponin, or CK-MB and troponin
- Echocardiography
  Perform echocardiography in reference to the Echo Core Laboratory Procedure to measure/evaluate the following items. The resulted echocardiographic images should be submitted to the Echo Core Laboratory.
  [Measurements/endpoints]
  Cardiac output, aortic valve pressure gradient (mean/maximum), EOA, EOAi*, aortic valve regurgitation (severity/regurgitation site), maximum blood flow rate, LVEF, left ventricular mass, LVMI*
  * Baseline BSA values must be used for calculation of EOAi and LVMI.
- QOL questionnaire
  - ○ EuroQOL (see Appendix 4)
  - ○ SF-12 (Appendix 5)
- Anticoagulant/antiplatelet drugs
- Blood purification
  Investigate the latest dialysis prior to the 1 year post-procedural follow-up visit.
- Other concomitant medication/therapy
- AE/device deficiency
  For a patient who has suffered a stroke, mRS must be evaluated within 30 to 90 days and beyond 90 days as earlier as from the onset of stroke.

### 10.3.8 Years 2 through 5 annual post-procedure visits

The tests/observation at 2 to 5 years post-procedural follow-up should be performed within the permissible time windows shown in Section 10.1 “Test/observation schedule” to collect the data on the following items.





- NYHA classification of cardiac performance (see Section 30 “GLOSSARY”)
- CCS status of stable angina (see Section 30 “GLOSSARY”)
- Echocardiography
  Perform echocardiography in reference to the Echo Core Laboratory Procedure to measure/evaluate the following items. The resulted echocardiographic images should be submitted to the Echo Core Laboratory.
  [Measurements/endpoints]
  Cardiac output, aortic valve pressure gradient (mean/maximum), EOA, EOAi*, aortic valve regurgitation (severity/regurgitation site), maximum blood flow rate, LVEF, left ventricular mass, LVMI*
  * Baseline BSA values must be used for calculation of EOAi and LVMI.
- QOL questionnaire
  - ○ EuroQOL (see Appendix 4)
  - ○ SF-12 (Appendix 5)
- Anticoagulant/antiplatelet drugs
- AE/device deficiency

### 10.3.9 At trial discontinuation and unscheduled visits

When a subject enrolled in continued access registry discontinues the trial, and if the subject made an unscheduled visit other than those specified in the protocol for necessity as specified in Section 10.2.9, collect the data in accordance with Section 10.2.10.





# 11 ADVERSE EVENT/DEVICE DEFICIENCY

## 11.1 Definition of Adverse Events

An AE is 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 study device. However, for an event occurred in persons other than the subjects, it should be limited to an event suspected to be associated with the use of the study device.

The observation period for AEs will be from the start of the study procedure through to the final follow-up observation visit. A disease developed between the time of informed consent and the start of the study procedure, which has not recovered at the start of the study procedure, should be handled as a pre-procedural complication.

## 11.2 Definition of Serious Adverse Events

An SAE is an event applicable to the followings, in accordance with the PMD Act Enforcement Regulations Article 274-2, irrespective of causal relationship to the study device.

(a) Death
(b) Those that may lead to death
(c) Those requiring inpatient hospitalization or prolongation of existing hospitalization for treatment
(d) Disability
(e) Those that may lead to disability
(f) Serious cases in accordance with those in (a) to (e)
(g) Any congenital disease or abnormality in the offspring of a treated patient

However, hospitalization without a newly developed AE or aggravated pre-procedural complication as shown in the followings is not regarded as an SAE, not requiring reporting to the sponsor.

- Hospitalization for treatment scheduled before the procedure (e.g.: hospitalization for surgery for pre-procedural complication that became possible due to improvement in the heart condition)
- Hospitalization for management (e.g.: regular checkup, hospitalization for examination, educational hospital admission)
- Admission to a rehabilitation facility

If an SAE is found, the investigators should take appropriate actions, and immediately report to the sponsor (see Section 11.5 “Serious Adverse Events Reporting”).

## 11.3 Adverse Events Associated with Laboratory Test Abnormal Variations

If any abnormal variations from baseline are found in the laboratory tests, blood pressure, and ECG as specified in the protocol, and if the value is applicable to the definition of SAE, or if the principal investigator or subinvestigators judges the value as an AE, the event should be handled as an AE. Also for a clinically important abnormal finding is found in the test items not specified in the protocol, and if the finding is applicable to the definition of SAE, or if the principal investigator or subinvestigators judges the finding as an AE, the finding should be handled as an AE.

## 11.4 Device Deficiencies

A device deficiency is defined as the failure of a device to meet its quality, safety, and performance specifications, such as damage and or malfunctioning, regardless of being associated with the design, supply, storage, or used.

## 11.5 Serious Adverse Event Reporting

If an SAE or defect that may cause an SAE is found after the start of the study procedure, the principal investigator or subinvestigators should take appropriate actions in accordance with the followings.

(1) The principal investigator or subinvestigators should take appropriate actions for the subject, and regardless of the causal relationship to the study device, immediately report the SAE or defect that may cause an SAE to the sponsor orally, via telephone, e-mail, or FAX.

(2) The investigator (if unavoidable, the subinvestigator under instructions from the investigator) should immediately report the details to the director of the study site and sponsor by forms such as “Report of serious adverse events”.

(3) If an event that was assessed as non-serious at the time was reassessed as serious later by additional information, etc., the investigator should take the above-mentioned actions (1) to (2).

After receiving the report from the principal investigator or subinvestigators, the sponsor should take the following actions.

(4) If the sponsor is aware of any defect unforeseeable from the Investigational Devices Brochure among SAEs or failure that may cause an SAE, the sponsor should immediately report it to the investigators and directors of all study sites.

(5) The sponsor will report a list of cases with an SAE that is suspected to be associated with the use of the study device or defect that may cause an SAE to the investigator and director of the study sites annually starting from the day of first notification of the study plan and within 3 months after the due





date of the annual reporting period.

(6) In accordance with the PMD Act Enforcement Regulations Article 274-2, the sponsor should promptly report an SAE or defect that may cause an SAE to Minister of Health, Labour and Welfare.

## 11.6 Records of Adverse Events

In the event of an AE, it should be recorded in the eCRF in accordance with the followings.

(1) The investigators should enter all AEs occurred during follow-up observation period in this clinical trial in the eCRFs. The investigators should enter the name of AEs. However, an extremely severe symptom is found in the diagnostic class, it should be entered as a separate event from the original diagnosis. If a definitive diagnosis cannot be clearly established, individual signs or symptoms should be recorded in the eCRF within 10 working days as a general rule.

(2) The principal investigator or subinvestigators must confirm the outcome of the AE found in a subject, regardless of the causal relationship to the study device.

(3) If an AE is found, the investigators should enter the followings in the eCRF.

(a) Event:
Enter the name of diagnosis as much as possible. If a definitive diagnosis cannot be clearly established, enter the signs or symptoms.

(b) Date of onset:
For subjective symptoms, enter the date of onset or exacerbation. For AEs based on the laboratory test abnormal variations, enter the date of consultation or test.

(c) Severity:
The severity of AEs will be assessed by the following 3 scales.

| | |
|---|---|
| Mild: | With signs or symptoms that do not interfere with daily activities, or transient not requiring treatment with no secondary disorders |
| Moderate: | Interferes with daily activities, or requires symptomatic treatments |
| Severe: | With symptoms causing a significant pain, which enables to lead daily life, or requiring treatments |

(d) Severity:
The severity of AEs will be assessed by the following classification. For definition of SAEs, see Section 11.2 “Definition of Serious Adverse Events”.

1. Serious
2. Non-serious

(e) Measures taken for the study device:





Choose either one of the following 3 actions taken for the study device:

1. No measures taken for the THV
2. Valve explants
3. Other action

(f) Other measures taken:
Record the other measures taken by the following classification:

1. No
2. Yes (measures taken)

(g) Outcome:
Choose either one of the following 6 outcomes for the AE:

1. Recovered
2. Resolving
3. Not recovered
4. Recovered with sequelae
5. Death
6. Unknown

(h) Cause of death (only AEs with outcome of death):
If the outcome of an AE is death, assess the cause of death by the following classification: See Section 30 “GLOSSARY - Death”.

1. Cardiovascular death
2. Non-cardiovascular death

(i) Date of outcome (date of the clinical course was confirmed):
Enter the date of the outcome was determined. For a death case enter the date of death, and for laboratory test abnormality enter the date of consultation or test as the date of outcome. If assessed as not recovered, regardless of whether or not related to the study device or study device implantation procedure, except for irreversible AEs or exacerbation of pre-existing complication, the event should be followed up until recovery as a general rule and make an additional report. If a persistent, irreversible AE, or exacerbation of pre-existing complication is determined to be unnecessary to perform follow-up investigation until recovery, enter the assessment in the comment field of the eCRF.

(j) Causal relationship to the study device and study procedure:
Assess the causal relationship to the study device or study procedure by the following classification:

Definitely related: Applicable to any one of the following a) to c)

a) Has a temporal relationship





b) The AE abates upon completion of device application or implantation procedure

c) The AE cannot be clearly explained by the subject’s condition or pre-procedural complication

| | |
|---|---|
| Possibly related: | There may be a temporal relationship between the AE and the study device or implantation procedure, or the subject’s condition can be reasonably explained. |
| Possibly unrelated: | The temporal relation is unlikely between the AE and the study device or implantation procedure. |
| Unrelated: | There is no relation between the AE and the study device or implantation procedure |

Except for events assessed as “Unrelated”, handle AEs as with the relationship to the study device or study procedure.

(k) Reason for the assessment result of “Unrelated” to the study device or study procedure:
For AEs that were assessed as “Unrelated” to the study device or study procedure, enter the reason for the assessment result by the following classification:

1. An event associated with physiological factors
2. A pre-existing event associated with the primary disease or exacerbation of complication
3. A transient and accidental event
4. An event associated with concomitant drug or concomitant therapy
5. Other

(l) Comment:
Enter the rationales for the judgment of the causal relationship of AEs to the study device or study procedure and the rationales for the judgement of abnormal laboratory test variations as an AE..

## 11.7 Follow-up Investigation of Adverse Events

The investigators must follow up AEs until recovery as a general result or disease condition is stabilized, except for the following cases, and must report the additional information on the disease condition resulted from the follow-up investigation to the sponsor.

- The principal investigator or subinvestigators judges that the outcome of the AE cannot be recorded because the AE is permanent with no prospect of recovery, etc.
- The AE is exacerbation of pre-existing complication.
- The subject is lost to follow-up.

- The principal investigator or subinvestigators judges that a follow-up investigation until recovery is unnecessary.

AEs sustained at the end of the clinical trial or discontinuation of the trial, except for the above-mentioned cases, should be followed up until recovery or the disease condition is stabilized.





# 12 MONITORING OF THE CLINICAL TRIAL BY DATA MONITORING COMMITTEE

To ensure the safety of the subjects and ensure the ethical and scientific validity of the conduct of this clinical trial, Data Monitoring Committee (DMC) independent from the study organization including the sponsor and study sites will evaluate the intermediate data during the trial. The DMC consists of at least 3 members, including physicians with expertise in the present disease area and study treatment and a clinical statistician, monitors as to whether the clinical trial is conducted safely and appropriately, and give advice and recommendations to the sponsor for changes to the protocol and as to whether the trial should be continued or not. The monitoring of this clinical trial by the DMC will be continued until the end of the enrollment in the continued access registry, and may be extended as needed. For DMC opening requirements and detailed activities and operating procedure, see "EWJ-003 Data Monitoring Committee Procedure."

When provision of information including autopsy records, etc. is requested by the DMC, the study sites should respond as much as possible.

# 13 EVALUATION BY THIRD-PARTY JUDGMENT ORGANIZATION

## 13.1 Clinical Event Adjudication Committee

To avoid bias among study sites and physicians, and to ensure consistent and objective evaluation, the major clinical events reported by the study sites will be assessed by Clinical Event Committee (CEC) that is independent from the study organization including the sponsor and study sites. The CEC consists of at least 1 member with expertise in this present disease area and study treatment, and at least 1 member with expertise in neurological disease area, and as shown below, performs review and adjudication of all death cases and cases with stroke occurred in all enrolled subjects in this clinical trial (including continued access registry) up to 1 year post-procedure. For CEC opening requirements and detailed activities and operating procedure, see "EWJ-003 Clinical Event Adjudication Procedure."

- Death

For all death cases reported by the study sites within 1 year post-procedure, the CEC will adjudicates the cause of death (cardiovascular or non-cardiovascular death) and the causal relationship to the study device and study procedure, in accordance with VARC-2 guideline[56] (see Section 30 "GLOSSARY").

- Stroke

For all stroke cases reported by the study sites within 1 year post-procedure, the CEC will adjudicates the events (disabling stroke or non-disabling stroke) and the causal relationship to the study device and study procedure, in accordance with VARC-2 guideline[56] (see Section 30 "GLOSSARY").





The study sites must submit source documents required for event adjudication by CEC of all death cases and cases with stroke occurred up to 1 year post-procedure via the monitor as much as possible. The source documents required for event adjudication are as shown in Table 13-1, but not limited to those. When provision of additional information is requested by the CEC, the study sites should respond as much as possible.

Table 13-1: Source documents required for event adjudication by CEC

| Time of death | Time of stroke onset |
|---|---|
| • Death certificate<br>• Autopsy record*<br>• Discharge record | • Head neuroimaging (head CT/MRI)*<br>• Medical record<br>• Medical record by a neurologist/neurosurgeon<br>• mRS |

* When available

## 13.2 Echo Core Laboratory

To avoid bias among study sites and physicians, and to ensure consistent and objective evaluation, the echocardiographic parameters including EOA will be measured and evaluated by an echocardiography core laboratory that is independent from the study organization including the sponsor and study sites. The echocardiography core laboratory will appropriately measure/evaluate the echocardiographic parameters including EOA of all enrolled subjects in this clinical trial (including the continued access registry), using the echocardiographic imaging data at baseline, 30 days post-procedure, 6 months post-procedure, and 1 to 5 years post-procedure annually. For details, see the "Echo Core Laboratory Procedure."

The study sites should provide the echocardiographic imaging data (CD-ROM or DVD) at baseline, 30 days post-procedure, 6 months post-procedure, and 1 to 5 years post-procedure annually to the Echo Core Laboratory via the monitor.





# 14 SUBJECT TREATMENT DISCONTINUATION

## 14.1 Subject Treatment Discontinuation

Enrolled subjects will continuously participate in the clinical trial until all follow-up observations specified in the protocol are completed. However, the following subjects should discontinue the trial.

- A subject or the legal representative requests discontinuation of the participation in the clinical trial.
- The principal investigator or subinvestigators judges that continued trial will be a disadvantage for subject's health condition.
- The study procedure has not been started.
- When the subject is exiting the operation room, the investigational valve has not been implanted.
- The investigational valve was removed.
- The subject died.
- Continued participation in the clinical trial was deemed difficult.
- The sponsor requests (continued trial was determined to be a disadvantage in the subjects).

## 14.2 Subject Treatment Discontinuation Procedure

When a subject discontinues participation in the clinical trial, the following procedure should be used.

(1) The investigators should enter the date of discontinuation, reason for discontinuation, AE incidence status, and drug therapy status in the eCRFs. To ensure the safety of discontinued subjects, all possible measures should be taken, appropriate treatment should be given, and also for the safety after discontinuation, perform follow-up investigation as much as possible.
(2) If a subject discontinued the trial due to a safety issue arise from an incidence of AE or worsened disease, the investigators enter it in the eCRF in accordance with Section 11 "ADVERSE EVENTS."
(3) If an AE is found at the time of discontinuation, the investigators should perform a follow-up investigation of the AE.
(4) The investigators should promptly inform the sponsor of the subject's treatment discontinuation.

## 14.3 Follow-up Investigation of Subjects with Missing Visits

If a subject miss the follow-up observation as specified in the protocol because the subject failed to visit, the investigators should contact the subject as much as possible to investigate the subject's health condition (confirmation of survival, the presence or absence of an AE). In such a case, enter the contact means, date of contact, subject's condition, and the reason for missing visit in the eCRF. When after trying to contact to the subject, but the subject could not be reached, enter the fact, date of contact, contact means the eCRF.

# 15 STATISTICAL ANALYSIS

## 15.1 Safety and Efficacy Analysis of EWJ-003

In this clinical trial, the safety and efficacy of EWJ-003 will be evaluated in subjects for whom the investigational valve was dilated at a nominal volume. Subjects in the bailout treatment registry in whom the THV could not be dilated at a nominal volume will not be included in the analysis set (see Section 15.2 “Bailout Treatment Registry Statistical Analysis”). Also subjects enrolled in the continued access registry will not be included in the analysis set for the safety and efficacy evaluation of EWJ-003 (see Section 15.3 “Statistical Analysis of the Continued Access Registry”).

### 15.1.1 Analysis sets

#### 15.1.1.1 Intent-to-treat analysis set

Regardless of whether or not the study procedure was given, or whether or not the study device was implanted, the intent-to-treat (ITT) analysis set is defined as an analysis population consists of all subjects enrolled in this clinical trial.

#### 15.1.1.2 As-treated analysis set

A subject population consisting of subjects who were enrolled in this clinical trial and implantation of the study device was initiated is defined as as-treated (AT) analysis set. The time when invasion such as incision was made on the access site is regarded as the start of the study procedure. The primary endpoint and secondary safety and efficacy endpoints will be analyzed in the AT analysis set.

#### 15.1.1.3 Valve implant analysis set

The subject population consisting for all subjects in whom the THV was implanted, and when the subject exited the operation room the implanted THV was maintained is defined as valve implant (VI) analysis set. Subjects for whom the investigational valve was not implanted, including subjects switching to surgery, and TAVI bioprosthetic valve other than the investigational valve was implanted, will not be included in the VI analysis set. As for subjects who received a valve-in-valve procedure, cases with additional investigational valve implantation will be included in the VI analysis set, while cases with additional TAVI bioprosthetic valve other than the investigational valve will be excluded from the VI analysis set. The secondary valve performance endpoints based on the echocardiographic evaluation will be analyzed in the VI analysis set.

### 15.1.2 Statistical analysis plan and statistical method

Mortality at 1 year post-procedure, the primary endpoint, will be analyzed in the AT analysis set to verify the non-inferiority of EWJ-003 therapy to the standard therapy. The non-inferiority test will be performed





using one-sided Fisher’s exact test, and at one-sided significant level of 0.05 if the 95% CI upper limit for the mortality at 1 year post-procedure is lower than the PG (45%), non-inferiority of EWJ-003 therapy to the standard therapy would be verified.

No statistical tests will be conducted for the secondary endpoints, but evaluate by descriptive statistics. The secondary valve performance endpoints based on the echocardiographic evaluation will be analyzed in the VI analysis set, and other secondary endpoints. Other data including subject background and baseline characteristics, and procedure information, etc. will be summarized by descriptive statistics.

All statistical analyses will be performed for, in addition to the entire analysis sets, each approach of TF, TA, and TAo. For continuous variables, the number of measurements, mean, standard deviation, median, quartile, minimum, maximum, and 95% CI of the mean will be calculated. On the other hand, for categorical variables, the number of samples (n), percentage (%), and for binary variables 95% CI will be calculated. For the primary endpoint and secondary safety and efficacy endpoints, the cumulative incidence will be calculated by Kaplan-Meier estimates as needed.

The detailed statistical analysis plan and statistical method are included in the Statistical Analysis Plan.

## 15.2 Bailout Treatment Registry Statistical Analysis

In this clinical trial, subjects enrolled in the bailout treatment registry will not be included in the analysis set for the safety and efficacy evaluation of EWJ-003. The bailout treatment registry will be analyzed separately as sub-analysis, which will primarily confirm the safety. In this sub-analysis, no statistical tests will be conducted.

## 15.3 Statistical Analysis of the Continued Access Registry

Subjects enrolled in the continued access registry will not be included in the analysis set for the safety and efficacy evaluation of EWJ-003. The continued access registry will be analyzed separately as sub-analysis, which will primarily confirm the safety. In this sub-analysis, no statistical tests will be conducted.

## 15.4 Creation/Changes to Statistical Analysis Plan

The person in charge of statistical analysis should create the Statistical Analysis Plan describing the statistical analysis plan and method for this clinical trial.

When the statistical analysis plan is to be changed, the sponsor will examine the validity of the change and impact on the evaluation in this clinical trial to decide whether or not the change should be made. When the statistical analysis plan should be changed, a revision history should be created describing the changes





made and reasons for the changes, and the Statistical Analysis Plan should be revised.

All deviations from the Statistical Analysis Plan should be described in the Study Report.





# 16 ELECTRONIC CASE REPORT FORM

## 16.1 Procedure for Electronic Case Report Form Creation and Precautions

(1) The investigators should create eCRFs using electronic data capture (EDC) system.

(2) The investigators should create an eCRF per subject.

(3) The appropriately trained investigator, subinvestigator, and/or study staff should enter the data that were collected in accordance with the protocol in the eCRFs. The eCRFs may be completed by, in addition to the investigator, those appointed in “List of subinvestigators/study staff. ”

(4) The sponsor will provide an explanation of entry and correction, in the eCRFs in accordance with “Guide for input into case report forms (eCRFs)”, to the investigator, subinvestigator, and/or study staff.

(5) The investigators should create an eCRF per subject after the end of observation as soon as possible (as a general rule within 10 working days), and submit it to the sponsor.

(6) The investigator should check the accuracy and validity of the data, and place name and a seal or sign the CRFs to be submitted to the sponsor.

(7) The sponsor will retain the original CRFs submitted by the investigator. The study site or investigator should retain a copy of the submitted CRFs.

## 16.2 Changes or Corrections to Electronic Case Report Forms

(1) For changes/corrections before placing the name and seal or signature, the relevant sites should be changed or corrected. However, for changes/corrections to an important content (considerations concerning informed consent, changes to abnormal variations, name of AEs and causality), reasons for changes/corrections should be described in the applicable field.

(2) For changes/corrections after placing the name and seal or signature, in addition to (1), place the name and a seal or sign again after the changes/corrections.

## 16.3 Inconsistency Between Electronic Case Report Form and Source Document

If any inconsistency is found between eCRF and source document, the investigator should create documents describing the contents and reasons for inconsistency. The investigator should place the name and a seal or sign the created document, and submit it to the sponsor. The investigator should retain a copy of the document.

## 17 PROTOCOL DEVIATIONS OR MODIFICATION

The principal investigator or subinvestigators must not make any changes or deviate from this protocol without prior written agreement with the sponsor and written approval based on the IRB's review. However, this is not applicable if it is medically evitable to eliminate immediate hazards to the subjects or only changes to the administrative matters in this clinical trial. The principal investigator or subinvestigators must record all protocol deviations whatever the reason may be. Of protocol deviations, deviations from the protocol to eliminate immediate hazards to the subjects or for other medically unavoidable reasons, the investigator must create records to explain the reasons and immediately submit the records to the sponsor and director of the study site. The principal investigator or subinvestigators may make any changes or deviate from this protocol without prior written agreement with the sponsor and written approval based on the IRB's review, if it is for medically unavoidable reasons such as to eliminate immediate hazards to the subjects. In such a case, if the deviation or change, and reasons and revision of the protocol are appropriate, the investigator must submit the proposal to the sponsor, director of the study site, and to the IRB via the director of the study site as soon as possible, and obtain a written agreement of the director of the study site and written agreement from the sponsor via the director of the study site. For any changes that may significantly affect the conduct of the clinical trial or may increase hazards to the subject, the investigator must promptly submit a report to the sponsor, director of the study site, and IRB via director of the study site.

## 18 TRIAL DISCONTINUATION/SUSPENSION AND TERMINATION

### 18.1 Discontinuation/Suspension of the Entire Trial

In the following cases, the sponsor will discuss with medical advisors to decide whether or not the entire clinical trial should be discontinued or suspended.

- Continued participation in the clinical trial is deemed difficult due to an incidence of unpredictable SAE.
- Occurrence of significant disease that may interfere with continued clinical trial, disorder, or death is reported.

Discontinuation or suspension of the entire clinical trial should be carried out in accordance with the following procedure.

(1) If discontinuation or suspension of the entire clinical trial is decided, the sponsor will immediately notify all directors of the study sites and the regulatory authority of the discontinuation or suspension and its reason in writing.

(2) When the sponsor decides and notifies discontinuation or suspension of the entire clinical trial, the





director of the study site should promptly notify the investigator and IRB in writing, and provide a written explanation about the discontinuation or suspension.

(3) If discontinuation or suspension of the entire clinical trial is decided, the investigator should promptly notify, and provide the subjects with appropriate medical care and take other necessary measures.

(4) When this clinical trial is discontinued or suspended, the study sites should return the study materials (study device, etc.) to the sponsor.

### 18.2 Discontinuation/Suspension at Individual Study Sites

In the following cases, the study sites should discontinue or suspend the clinical trial.

- The investigator judges that the clinical trial should be discontinued.
- The director of the study site or IRB judges that the clinical trial should be discontinued.
- The sponsor judges that a violation of the J-GCP, protocol, or clinical trial contract by the study site hindered proper conduct of the clinical trial.

Discontinuation or suspension of the clinical trial at individual study sites should be carried out in accordance with the following procedure.

(1) Discontinuation or suspension decided by the investigator
If the investigator discontinues or suspends this clinical trial at the his/her discretion, the investigator should promptly notify the director of the study site of discontinuation or suspension and reasons in writing. When the investigator decides and notifies discontinuation or suspension of the clinical trial, the director of the study site should promptly notify the IRB and sponsor of discontinuation or suspension and reasons in writing.

(2) Discontinuation or suspension decided by the director of the study site or IRB
The director of the study site should promptly notify the sponsor, investigator, and IRB, of the decision of discontinuation or suspension at the discretion of the director or IRB in writing.

(3) Discontinuation or suspension decided by the sponsor
When the sponsor decides and notifies discontinuation or suspension of the clinical trial, the director of the study site should promptly notify the investigator and IRB in writing, and provide a written explanation about the discontinuation or suspension.

In any of the above cases, the sponsor will promptly notify all directors of the study sites and the regulatory authority of the discontinuation or suspension and its reason in writing. If discontinuation or suspension of the clinical trial is decided, the investigator should promptly notify, and provide the subjects with





appropriate medical care and take other necessary measures. The study sites should return the study materials (study device, etc.) to the sponsor.

### 18.3 Termination of the Clinical Trial

When the number of enrolled subjects in this clinical trial reached the target number of subjects specified in the protocol, and at the time point when the last subject completed follow-up observation at 5 years post-procedure or when this clinical trial is prematurely discontinued, the entre clinical trial is considered to be completed. However, in this clinical trial, study report will be created at the time point when the data on the EWJ-003 analysis set up to 1 year post-procedure have been collected, which should be attached to the approval application for the purpose of the expanded indications of EWJ-003, and therefore even before the last subject completes follow-up observation at 5 years post-procedure, acquisition of marketing approval for EWJ-003 may be regarded as completion of this clinical trial. In such a case, this clinical trial will be switched to a post-marketing clinical trial after acquisition of the marketing approval, and will be continued until completion of follow-up observation at 5 years post-procedure by the last subject. (See Section 28 "CONSIDERATION AFTER MARKETING APPROVAL").

Completion of this clinical trial at study site should be carried out in accordance with the following procedure.

(1) When the clinical trial is completed at the study site, the investigator should promptly notify the director of the study site of completion of the trial in writing, and report the summary of the trial results in writing based on the regulations of the study site.

(2) When the investigator notifies completion of the clinical trial, the director of the study site should promptly notify the IRB and sponsor in writing, and report the summary of the trial results based on the submitted report by the investigator.

(3) The sponsor will carry out the procedure for completion of the clinical trial at the study site. The investigator and director of the study site should carry out the procedure for completion of the clinical trial in accordance with the regulations of the study site.

(4) When this clinical trial is completed, the study site should return all the study materials (study device, etc.) to the sponsor.

## 19 RECORD RETENTION

### 19.1 Study Site

The record keeping manager appointed by the director of the study site will maintain essential documents concerning the clinical trial to be retained in the study site as specified in the J-GCP for either of the





following period (1) or (2), whichever comes later.

(1) The date of marketing approval of the study device (or 3 years following the date that the Sponsor notified the decision not to attach the documents of the study results as specified in the J-GCP Article 32-3 to the marketing approval application form as specified in the PMD Act Article 23-2-5 Section 3)
(2) Three years after discontinuation or completion of the clinical trial.

However, if the record retention period provided above becomes difficult for the reason of the study site or extended per request by the sponsor, the sponsor and the study sites will discuss the duration and method of retention.

The investigator must retain the trial-related documents and records in accordance with the instructions given by the director of the study site. The records subject to storage include letters to the sponsor, documents for the meetings, and communications via telephone about important considerations related to the trial.

### 19.2 Sponsor

The sponsor will maintain all study records to be retained as specified in the J-GCP for either of the following period (1) or (2), whichever comes later:

(1) Five years after the day of marketing approval for the medical device related to the study device in this clinical trial (or, 3 years after the day when discontinuation of the development of the device was decided).
(2) Three years after discontinuation or completion of the clinical trial.

If retention of the trial-related records to be retained by the founder of IRB and director of the study site becomes unnecessary, the sponsor will notify the founder of IRB and director of the study site.

## 20 TRAINING

The investigators must complete the training course provided by the sponsor. The training course includes trainings for the protocol, eCRFs, and study device, and the investigators must not perform the study procedure before completion of these trainings. The subjects for each training program are as shown in Table 20-1.

Table 20-1: Training subjects

| Training program | Training subjects |
|---|---|
| Training for the protocol | All investigators, subinvestigators, and study staff |
| Training for eCRFs | Investigators, subinvestigators and/or study staff who will enter the data in eCRFs |
| Training for the study device | Investigators, subinvestigators, and study staff, who will be engaged in the study procedure |

Since the TF system, the study device, already has been approved in Japan, if completed the training for the transfemoral system prior to the use in clinical practice, re-training would not be required. As for the training for the TA/TAo systems, all investigators, subinvestigators, and study staff must complete the training course before performing the study procedure using the relevant system. Records of training will be documented and retained by the sponsor.





# 21 DIRECT ACCESS TO SOURCE DOCUMENTS

## 21.1 Identification of Source Documents

Source documents are records required for reproduction and evaluation of the course of the trial, such as subject's medical records, the study device use records, etc. Of the data recorded in eCRFs, records of the following items in the eCRFs may be handled as source documents.

(1) Descriptions of AEs (severity, seriousness, causality, outcome, cause of death, treatments given, and comments)
(2) Descriptions of defects (name of defect, detailed information on defect)
(3) Date and reason for discontinuation
(4) Follow-up investigation of subjects with missing visits
(5) Descriptions of concomitant drug/therapy
(6) Clinical decisions and views of the principal investigator or subinvestigators

## 21.2 Procedure for Direct Access

The director of the study site and investigator should accept and cooperate in monitoring and audits by the sponsor as well as an investigation by the IRB and regulatory authority. In such cases, upon requests by the monitor, auditor, IRB, and regulatory authority, provide all trial-related records including source documents for direct access. The sponsor will discuss with the investigator and director of the study site about the direct access procedure, timing, and items to be reviewed, and then directly access to the documents for review.

# 22 CLINICAL TRIAL QUALITY CONTROL AND QUALITY ASSURANCE

## 22.1 Quality Control

In order to ensure that the clinical trial, data generation, and reporting are conducted in compliance with the J-GCP and protocol, quality control of the clinical trial should be performed by the monitor and personnel in charge of quality control and data management at each stage of the trial.

### 22.1.1 Clinical trial monitoring

In order to ensure that attempts are made for protection of subjects' rights, retention of the safety, and improved welfare, the trial is conducted in compliance with the latest protocol and J-GCP, and the trial data reported by the principal investigator or subinvestigators are accurate and complete and can be verified based on the trial-related records including source documents, the monitor should visit the study sites in accordance with the pre-specified procedure and directly access to the source documents to perform





monitoring of the clinical trial.

## 22.2 Quality Assurance

In order to confirm that the clinical trial was conducted in compliance with the J-GCP, standard operating procedure, protocol, and pre-specified other plans and procedures, the quality of the clinical trial should be assured by the auditor of the sponsor. The auditor should be independent from monitoring and quality control of the clinical trial, perform an audit in accordance with the pre-specified audit plan and procedure, and confirm proper conduct of the clinical trial, including reliability of the data, to assure the quality of the clinical trial.

# 23 STUDY DEVICE MANAGEMENT

The study sites and sponsor should appropriately control the study device in accordance with the following considerations.

(1) Provision of study device control procedure
The sponsor will provide the study sites with study device control procedure that specifies handling of the study device, records, management, and storage, without delay after conclusion of the contract.

(2) Delivery of the study device
After conclusion of the contract between the study site and sponsor, the sponsor will deliver the study device to the study site.

(3) Storage, recovery, control records of the study device, and confirmation of unused device
The study device should be stored and controlled by the director of the study site or study device manager appointed by the director of the study site in accordance with the study device control procedure. The director of the study site or study device manager should carry out the storage, recovery, control records of the study device, and confirmation of unused device in accordance with the followings.

(a) The study device must be appropriately stored and controlled in accordance with the study device control procedure.
(b) In order to understand the use status of the study device and progress of the clinical trial, create a study device log for recording. The study device log includes the date, number of device, manufacturing number or manufacturing code, expiration date, product number of the device, and subject ID code.
(c) Any expired unused device must be returned to the sponsor. Also any study device with trouble or deficiency should be returned to the sponsor as much as possible.





(4) Consistency check on the control records of the study device and input in the eCRFs
The investigator and study device manager should check the consistency between the contents of study device log and eCRFs, and if any inconsistency is found, the cause should be investigated immediately, and take necessary measures. Corrections should be made so as to the correction history can be seen. Also check the contents of the study device log, and if any inconsistency is found, take necessary measures.

# 24 ETHICAL CONSIDERATIONS AND REGULATORY REQUIREMENTS

## 24.1 Compliance with J-GCP

This clinical trial will be conducted in compliance with the PMD Act, ethical principles that have their origin in the Declaration of Helsinki, the J-GCP, ministerial ordinances partially amending J-GCP and the relating regulations, and this protocol.

## 24.2 Creation of Written Patient Information and Informed Consent Form

(1) The investigator, with the cooperation of the sponsor, should create the written patient information and informed consent form. Creation and revision of the written patient information should be carried out in compliance with the ethical principles based on the J-GCP. For the written patient information, use plain terms so that subjects can easily understand.

(2) The written patient information and informed consent form should include the followings:

(a) That the clinical trial involves research.
(b) The purpose of the trial.
(c) The name, job title, and contact place of the principal investigator or subinvestigators.
(d) The trial procedures to be followed (experimental aspects of the trial, subject inclusion criteria, and exclusion criteria).
(e) The reasonably expected benefits and risks or inconveniences to the subject.
(f) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
(g) The expected duration of the subject's participation in the trial.
(h) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time. By refusing to participate or withdrawing from the trial, the subject will not get a penalty or loss of benefits to which the subject is otherwise entitled.
(i) Handling of the study device in case where the subject withdraws from the trial after participation in the trial.
(j) That the monitor, auditor, IRB, and regulatory authority will be granted direct access to the subject's original medical records. In such a case, the subject's confidentiality will be protected. By signing a written informed consent form, the subject is authorizing such access.
(k) If the results of the trial are published, the subject's identity will remain confidential.
(l) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
(m) The compensation and treatment available to the subject in the event of trial-related injury.





(n) The approximate number of subjects involved in the trial.
(o) That the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
(p) The foreseeable circumstances or reasons under which the subject's participation in the trial may be terminated.
(q) The anticipated expenses, if any, to the subject for participating in the trial.
(r) The anticipated payment, if any, to the subject for participating in the trial (arrangement of prorated payment, etc.)
(s) The subject's responsibilities.

## 24.3 Changes to the Protocol, Written Patient Information, and Informed Consent Form

If any changes are to be made to the protocol, the sponsor will discuss with the investigator, promptly revise the protocol, and submit the revised protocol to the director of the study sites to gain an approval of the IRB. The investigator must not conduct the clinical trial under the revised protocol without an approval of the IRB.

If any important information becomes available that affects the subject's consent to participation in the trial, or if revision of the protocol results in changes to the written patient information and informed consent form, the investigator must revise the written patient information and informed consent form based on the new information, and gain an approval of the IRB before use of the revised documents. The principal investigator or subinvestigators must provide the subject with an explanation using the revised written patient information, and obtain written informed consent to continued participation in this clinical trial voluntarily signed by the subject. In such cases where the subject is difficult to give written reconsent, the subject may continue the study participation by obtaining consent from the legal representative.

## 24.4 Institutional Review Board

Prior to the conduct of this clinical trial, the IRB must review and approve whether the study site is suitable for the conduct of the trial, based on the protocol, written patient information and informed consent form, study device investigator's brochure, and other necessary documents, from the standpoints of ethical, scientific, and medical validity. Changes to the protocol, written patient information, and informed consent form must be approved by the IRB prior to the application of the changes.

If the duration of the trial exceeds 1 year, the study site must be reviewed by the IRB as to whether or not the trial should be continued at least once per year, and must be approved by the IRB. Also cases where a serious, unforeseeable defect was reported, whether or not the trial should be continued at the study site





should be reviewed.

## 24.5 Considerations Concerning Subject's Privacy

(1) The investigators should enter the subject's ID code in the eCRFs, with no medical record number. If other documents/materials have expressions by which the subject can be personally identified, such as subject's name, the expressions will be removed before submission of the documents/materials to the sponsor.

(2) The principal investigator or subinvestigators should provide the subject with the information that when the monitor, auditor, IRB, and regulatory authority directly access to the trial-related records, when the trial-related records are used for marketing approval application for the study device, and when the trial results are published, the confidentiality of the subject will be protected.

## 24.6 Compensation Available to the Subjects

The sponsor will prepare the compensation system in case of subject's health injury. In the event of trial-related health injury, based on the sponsor's compensation system, medical expenses, medical allowance, and compensation will be paid. However, this does not apply if the damage is willful or gross negligence of the study site, or subject's deliberate damage.

## 24.7 Payment to Reduce Financial Burden on the Subjects

As for the payments to reduce financial burden on the subjects for participation in the trial, based on the contract with each study site, the sponsor will pay to the study site at the pre-specified time point.

# 25 AGREEMENT TO PROTOCOL

The investigator and sponsor will sign the written agreement in the protocol to certify the agreement on the contents of the protocol, and agreement on the compliance with the protocol.

# 26 USE OF STUDY RESULTS OR PUBLICATION POLICY

(1) Unpublished information provided by the sponsor, including all information on the study device and other academic data concerning the clinical use, components, performance, and principle of the study device should be kept confidential. The principal investigator or subinvestigators must use the above information only for the purpose of this clinical trial, and must not use for other purpose without prior written approval by the sponsor.

(2) By signing the written agreement in the protocol, the investigator agrees with the sponsor to use the trial results for marketing approval application in Japan, publishing, and for the information for medical experts.





# 27 SCHEDULED TRIAL DURATION

Scheduled trial duration: September 2016 to September 2025*

<EWJ-003 analysis set/bailout treatment registry> [End of subject enrollment]
Scheduled trial duration: September 2016 to December 2022
Scheduled duration of subject enrollment: September 2016 to October 2017 (for 14 months)

<Expanded clinical trial registry>
Scheduled trial duration: January 2018 to September 2025
Scheduled duration of subject enrollment: January 2018 to July 2020 (for 2 years and 6 months)**

* For this clinical trial, at the time point when the collection of data on the EWJ-003 analysis set up to 1 year post-procedure is completed, a study report will be created, which will be attached to the approval application form for the expanded indications of EWJ-003. Therefore, this clinical trial may be completed by acquisition of marketing approval of EWJ-003 prior to completion of the last subject follow-up observation at 5 years post-procedure.
** Subject entry into the continued access registry will be started after completion of subject entry into the EWJ-003 analysis set, and the subject enrollment will be continued until acquisition of marketing approval for EWJ-003.

# 28 CONSIDERATION AFTER MARKETING APPROVAL

This clinical trial will be completed at acquisition of marketing approval of the study device and will be switched to post-marketing clinical trial after marketing approval. Therefore, "clinical trial" in this clinical protocol and CRFs will be replaced with "post-marketing clinical trial" as needed. Additionally, "Japan Ministerial Ordinance on Good Clinical Practice for Medical Devices (Ordinance of the Ministry of Health, Labour and Welfare No. 36 of 2005)" shall be deemed to be replaced with "Japan Ministerial Ordinance on Good Clinical Practice for Medical Devices (Ordinance of the Ministry of Health, Labour and Welfare No. 36 of 2005) and Japan Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices (Ordinance of the Ministry of Health, Labour and Welfare No. 38 dated March 23, 2005)." (However, this section does not replace them.)

For the procedure to be followed at completion of the trial by acquisition of marketing approval for the study device, see Section 18.3.

## 29 GENERAL STUDY ORGANIZATION

Study sites

Name: Osaka University Hospital

Address: [redacted]

Contact to: [redacted]

Name: Keio University Hospital

Address: [redacted]

Contact to: [redacted]

Sponsor

Name: Edwards Lifesciences Corporation

Address: [redacted]

Contact to: [redacted]

Contract Research Organization

Name: [redacted]

Address: [redacted]

Contact to: [redacted]

For the details see Attachment 1 “General Study Organization.”





## 30 GLOSSARY

The definitions of terms used in this clinical trial are listed below:

| Term | Definition | Reference/rationale |
|---|---|---|
| Legally acceptable representative | A legally acceptable representative is who excersise parental authority over the subject, may also be the spouse, the guardian or the equivalent. | J-GCP |
| Adverse event | An adverse event (AE) is 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 study device. However, for an event occurred in persons other than the subjects, it should be limited to an event suspected to be associated with the use of the study device.<br><br>In this clinical trial, any events developed between the start of the study procedure and the final follow-up observation (when the trial is discontinued, until the time of discontinuation) will be regarded as AEs, and events occurred between the time of informed consent and the start of the study procedure, which have not recovered at the start of the study procedure, should be handled as pre-procedural complications. | J-GCP |
| Serious adverse event | A serious adverse event (SAE) is an event applicable to the followings, irrespective of causal relationship to the study device.<br><br>(a) Death<br>(b) Those that may lead to death<br>(c) Those requiring inpatient hospitalization or prolongation of existing hospitalization for treatment<br>(d) Disability<br>(e) Those that may lead to disability<br>(f) Serious cases in accordance with those in (a) to (e)<br>(g) Any congenital disease or abnormality in the offspring of a treated patient<br><br>However, hospitalization without a newly developed AE or aggravated pre-procedural complication as shown in the followings is not included in SAEs.<br><br>• Hospitalization for treatment scheduled before the procedure (e.g.: hospitalization for surgery for pre-procedural complication that became possible due to improvement in the heart condition)<br>• Hospitalization for management (e.g.: regular checkup, hospitalization for examination, educational hospital admission)<br>• Admission to a rehabilitation facility | Pharmaceutical and Medical Device Act Enforcement Regulation |
| Access site | The site where a guidewire, catheter, or sheath was inserted, including the artery or vein, left ventricular apex, and aorta. | |
| Access-related complication | An adverse clinical course that may have occurred in association with all access sites used during the study procedure. | |
| Access site/access-related complications | Access site/access-related complications are classified by the severity into severe vascular complications or mild vascular complications. | VARC-2 |





| Term | Definition | Reference/rationale |
|---|---|---|
| | • **Severe vascular complications**<br>○ Aortic dissection, aortic rupture, aortic annulus rupture, left ventricular perforation, apical aneurysm/pseudoaneurysm<br>○ Access site or access-related vascular injury (dissociation, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, unsuccessful percutaneous closure device) that caused death, life-threatening or severe hemorrhage, visceral ischemia, or neurological disorder<br>○ Embolization of the distal blood vessel (excluding the cerebral blood vessels) requiring surgery, or leading to amputation or irreversible peripheral organ damage<br>○ Unscheduled peripheral arterial intervention or surgery related to death, severe hemorrhage, visceral ischemia, or neurological disorder<br>○ Hypoperfusion of blood flow determined by the subject’s symptoms, physical findings and/or lower extremity angiography, or newly found ipsilateral limb ischemia diagnosed by no perfusion<br>○ Surgery for access-site related nerve injury<br>○ Nerve injury related to a permanent access site<br><br>• **Mild vascular complications**<br>○ Access site or access-related vascular injury (dissociation, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, unsuccessful percutaneous closure device) that does not cause death, life-threatening or severe hemorrhage, visceral ischemia, or neurological disorder<br>○ Embolization of the distal blood vessel treated with embolectomy and/or thrombectomy, without amputation or irreversible peripheral organ damage<br>○ Unscheduled peripheral arterial intervention or surgery not applicable to the definition of severe vascular complications.<br>○ Vascular repair (surgery, ultrasound-guided compression method, transcatheter arterial embolization, stent-graft placement) was performed or required | |
| Unsuccessful percutaneous closure device | Hemostasis of the arteriotomy site using a percutaneous closure device failed, and an alternative measure (excluding manual compression or auxiliary peripheral balloon angioplasty) was taken. | VARC-2 |





| Term | Definition | Reference/rationale |
|---|---|---|
| Aortic stenosis (AS) | Aortic stenosis is a condition of blood inflow from the left ventricle to the ascending aorta associated with aortic valve stenosis, and when the following criteria (a) and (b) were met, it is classified as severe.<br><br>(a) Mean pressure gradient ≥ 40 mmHg or aortic flow velocity ≥ 4.0 m/s<br>(b) AVA ≤ 1.0 $cm^2$ or AVA index ≤ 0.6 $cm^2/m^2$<br><br><Severity classification of AS><br>Guideline: Mild / Moderate / Severe<br>Maximum aortic flow velocity (m/s): < 3.0 / 3.0 - 3.9 / ≥ 4.0<br>Mean systolic pressure gradient (mmHg): < 25 / 25 - 39 / ≥ 40<br>AVA ($cm^2$): > 1.5 / 1.1 - 1.5 / ≤ 1.0<br>AVA index ($cm^2/m^2$): --- / --- / ≤ 0.6 | ACC/AHA, Guidelines for Surgical and Interventional Treatment of Valvular Heart Disease |
| Aortic valve regurgitation | It is an index that reflects the total volume of blood leaked into the left ventricle, including both transvalvular regurgitation and paravalvular regurgitation. The severity of aortic valve regurgitation will be assessed in accordance with the followings:<br><br><Severity classification of aortic valve regurgitation><br>Mild / Moderate / Severe<br>Semi-quantitative evaluation<br>Diastolic retrograde wave of the descending aorta: None or proto-diastole / Middle part of a diastole / Significant, for the entire diastolic phase<br>Range of paravalvular regurgitation (%): < 10 / 10 - 29 / ≥ 30<br>Quantitative evaluation<br>Regurgitation volume (mL/beat): < 30 / 30 - 59 / ≥ 60<br>Regurgitation rate (%): < 30 / 30 - 49 / ≥ 50<br>Effective regurgitant orifice area ($cm^2$): 0.10 / 0.10 - 0.29 / ≥ 0.30 | VARC-2 |
| Aortic valve regurgitation | At the Echo Core Laboratory, the severity of aortic valve regurgitation will be assessed in accordance with the followings:<br><br><Severity classification of aortic valve regurgitation><br>7-grade evaluation / Corresponding 4-grade evaluation: ASE / VARC-2 / Regurgitation volume (mL/beat) / Regurgitation rate (%) / Effective regurgitant orifice area ($mm^2$)<br>None: 0 / None/negligible / Unable to quantitate/undetectable<br>Negligible: 1<br>Mild: 2 / Mild / < 15 / < 15 / < 5<br>Mild - Moderate: 2 / Mild / 15 - 29 / 15 - 29 / 5 - 9<br>Moderate: 3 / Moderate / 30 - 44 / 30 - 39 / 10 - 19<br>Moderate - Severe: 3 / Moderate / 45 - 59 / 40 - 49 / 20 - 29<br>Severe: 4 / Severe / ≥ 60 / ≥ 50 / ≥ 30 | |

<table>
<tr><th>Term</th><th>Definition</th><th>Reference/rationale</th></tr>
<tr><td>Aortic valve incompetence</td><td>A condition where the aortic valve does not close properly, with blood regurgitation from the aortic valve into the left ventricle, and the severity will be assessed in accordance with the followings:<br><br><Severity classification of aortic valve incompetence><br><table><tr><th></th><th>Mild</th><th>Moderate</th><th>Severe</th></tr><tr><td colspan="4">Qualitative evaluation</td></tr><tr><td>Aortographic grade</td><td>I</td><td>II</td><td>III - IV</td></tr><tr><td>Color Doppler jet area</td><td>< 25% of LVOT</td><td></td><td>> 65% of LVOT</td></tr><tr><td>vena contracta width (cm)</td><td>< 0.3</td><td>0.3 - 0.6</td><td>> 0.6</td></tr><tr><td colspan="4">Quantitative evaluation (catheter or echo)</td></tr><tr><td>Regurgitation volume (RVol) (mL/beat)</td><td>< 30</td><td>30 - 59</td><td>≥ 60</td></tr><tr><td>Regurgitation rate (%)</td><td>< 30</td><td>30 - 49</td><td>≥ 50</td></tr><tr><td>Effective regurgitant orifice area (cm²)</td><td>0.10</td><td>0.10 - 0.29</td><td>≥ 0.30</td></tr></table></td><td>ACC/AHA, Guidelines for Surgical and Interventional Treatment of Valvular Heart Disease</td></tr>
<tr><td>Prosthetic valve stenosis</td><td>When meeting both of the following criteria (a) and (b), and meeting either one of (a) or (b) and (c), it is regarded as significant stenosis.<br><br>(a) Maximum aortic flow velocity ≥ 3.0 m/s or mean pressure gradient ≥ 20 mmHg<br>(b) EOA ≤ 1.1 cm² (when BSA ≥ 1.6 cm²), or ≤ 0.9 cm² (when BSA < 1.6 cm²)<br>(c) Aortic flow velocity coefficient by continuous wave Doppler method ≤ 0.35<br><br><table><tr><th></th><th>Normal</th><th>Mild</th><th>Moderate/ Severe</th></tr><tr><td colspan="4">Quantitative evaluation [blood flow dependent]</td></tr><tr><td>Maximum aortic flow velocity (m/s)</td><td>< 3.0</td><td>3 - 4</td><td>> 4</td></tr><tr><td>Mean pressure gradient (mmHg)</td><td>< 20</td><td>20 - 40</td><td>> 40</td></tr><tr><td colspan="4">Quantitative evaluation [blood flow independent]</td></tr><tr><td>Aortic flow velocity coefficient by continuous wave Doppler method*</td><td>> 0.35</td><td>0.35 - 0.25</td><td>< 0.25</td></tr><tr><td>EOA (cm²) [BSA ≥ 1.6 cm²]</td><td>> 1.1</td><td>1.1 - 0.8</td><td>< 0.8</td></tr><tr><td>EOA (cm²) [BSA < 1.6 cm²]</td><td>> 0.9</td><td>0.9 - 0.6</td><td>< 0.6</td></tr></table>* When the LVOT > 2.5 cm, the significant stenosis criterion is < 0.20.</td><td>VARC-2</td></tr>
<tr><td>As-treated analysis set</td><td>A subject population consisting of subjects who were enrolled in this clinical trial and implantation of the study device was initiated is defined as as-treated (AT) analysis set.</td><td></td></tr>
<tr><td>Bleeding</td><td>Bleeding can be classified into life-threatening or disabling, severe, and mild by severity.<br><br>• Life-threatening or disabling bleeding<br>When applicable to any one of the followings:<br>○ Fatal bleeding (BARC Type 5)<br>○ Bleeding of major organs (BARC Types 3b and 3c, including intracranial hemorrhage, intramedullary hemorrhage, intraocular hemorrhage, pericardial bleeding requiring pericardial puncture, and muscle hemorrhage with compartment syndrome.<br>○ Hypovolemic shock or bleeding that induced severe</td><td>VARC-2</td></tr>
</table>





<table>
<tr><th>Term</th><th>Definition</th><th>Reference/rationale</th></tr>
<tr><td></td><td>hypotension requiring vasoconstrictors or surgery.<br>○ A decrease in hemoglobin ≥ 5 g/dL, or apparent bleeding with transfusion of whole blood preparation or red cell product ≥ 4 units* (BARC Type 3b)<br><br>• Severe bleeding (BARC Type 3a)<br>Not applicable to the definition of life-threatening or disabling bleeding, and any one of the following is observed:<br>○ Bleeding with a decrease in hemoglobin ≥ 3.0 g/dL<br>○ Bleeding with transfusion of 2 or 3 units whole blood preparation or red cell product<br>○ Bleeding causing hospitalization or a permanent injury<br>○ Bleeding requiring surgery<br><br>• Mild bleeding (BARC Type 2 or 3a, severity dependent)<br>Not applicable to the definition of life-threatening or disabling bleeding or severe bleeding, and all bleedings assessed as of clinical significance (e.g.: access site hematoma)<br><br>* Considering a predicted increase in hemoglobin of 1 g/dL per unit of general red cell preparation, the reduced hemoglobin level may be estimated</td><td></td></tr>
<tr><td>CCS status of stable angina</td><td>Class 1: No limits to physical activities. Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.<br>Class 2: Slight limitation of ordinary activity. Angina with walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the 1 to 2 hours after awakening. Or walking more than two blocks on the level and climbing more than two flight of ordinary stairs at a normal pace and in normal conditions.<br>Class 3: Marked limitation of ordinary activity. Angina with walking one or two blocks (80 m - 160 m) on the level and climbing one flight of stairs in normal conditions and at normal pace.<br>Class 4: Inability to carry on any physical activity without discomfort. Anginal symptoms may be present at rest.</td><td>CCS</td></tr>
<tr><td>Cancer</td><td>Refers to a condition caused by an uncontrolled division of abnormal cells conditions, and is characterized by invasion into the surrounding tissues, and can progress to distant metastasis. Cancer is classified into benign and malignant, and in this clinical trial, if a subject has a history of malignant cancer, enter as a subject with a history of cancer at baseline in the eCRF.</td><td></td></tr>
<tr><td>Cardiac tamponade</td><td>Newly occurred pericardial effusion associated with hemodynamic instability and a clear causal relationship to the study procedure.</td><td>VARC-2</td></tr>
<tr><td>Conduction disorder/arrhythmia</td><td>The following data on conduction disorder/arrhythmia will be collected:<br><br>• Conduction disorder at baseline, paroxysmal or persistent atrial fibrillation/flutter, and permanent pacemaker implantation<br>• New or aggravated conduction disorder related to the implanted valve</td><td>VARC-2</td></tr>
</table>





<table>
<tr><th>Term</th><th>Definition</th><th>Reference/rationale</th></tr>
<tr><td></td><td>○ First degree atrioventricular (A-V) block<br>○ Second degree A-V block (Mobitz type I or II)<br>○ Third degree A-V block<br>○ Incomplete right bundle branch block<br>○ Right bundle branch block<br>○ Defect intraventricular conduction<br>○ Left bundle branch block<br>○ Left anterior hemiblock (LAH)<br>○ Left posterior hemiblock (LPH)<br>○ Block requiring permanent pacemaker implantation<br>• Persistent or transient advanced A-V block<br>When advanced A-V block is observed at every test, it is regarded as persistent.<br>• New permanent pacemaker implantation<br>The indications of permanent pacemaker implantation and the number of days after the procedure should be accurately recorded.<br>• Newly found atrial fibrillation/flutter<br>• Newly found arrhythmia with hemodynamic instability or requiring treatments</td><td></td></tr>
<tr><td>Switching to surgery</td><td>Refers to cases with switching to open heart surgery by sternotomy due to a procedure-related complication during the study procedure.</td><td>VARC-2</td></tr>
<tr><td>Coronary obstruction</td><td>During the study procedure or post-procedure newly found prosthetic valve, native cusp, lump lime, or partial or total occlusion at the coronary ostium associated with dissociation in the angiogram or echocardiography findings.</td><td>VARC-2</td></tr>
<tr><td>Death</td><td>Death is classified into cardiovascular death or non-cardiovascular death by the cause of death.<br><br>• Cardiovascular death<br>When applicable to the followings, it is regarded as cardiovascular death:<br>○ Death directly associated with the heart (e.g.: myocardial infarction, cardiac tamponade, worsened heart failure)<br>○ Death associated with blood vessels other than the coronary artery (e.g.: neurological event, pulmonary embolism, aortic aneurysm rupture, dissecting aneurysm, and other vascular disease)<br>○ All study procedure-related deaths, including deaths related to procedural complication and treatments for the procedural complication.<br>○ All deaths related to the investigational valve, including deaths from structural valve deterioration, non-structural dysfunction, and other valve-related AEs.<br>○ Sudden death and unwitnessed death<br>○ Death with unknown cause<br><br>• Non-cardiovascular death<br>It is apparent that the major cause of death is a disease other than the above (e.g.: trauma, cancer, suicide)</td><td>VARC-2</td></tr>
<tr><td>Device deficiency</td><td>A device deficiency is defined as the failure of a device to meet its quality, safety, and performance specifications, such as damage and or malfunctioning, regardless of being associated with the design, supply, storage, or used.</td><td>J-GCP</td></tr>
<tr><td>Valve malposition</td><td>Valve malposition includes moved valve, valve embolism, and implantation at an unintended site. For definition of events, see respective section.</td><td>VARC-2</td></tr>
</table>





<table>
<tr><th>Term</th><th>Definition</th><th>Reference/rationale</th></tr>
<tr><td>Moved valve</td><td>After a prosthetic valve was placed in an appropriate position, the valve moved upward or downward in the aortic annulus from the implanted site, with or without a causal relationship to the study procedure.</td><td>VARC-2</td></tr>
<tr><td>Valve embolism</td><td>The prosthetic valve moved during or after implantation, and no longer stay in the annulus.</td><td>VARC-2</td></tr>
<tr><td>Implantation at an unintended site</td><td>A prosthetic valve being persistently implanted at the site other than the aortic root.</td><td>VARC-2</td></tr>
<tr><td>Device success</td><td>No operative death (death within 30 days post-procedure or death during hospital stay), the investigational valve was implanted at an appropriate anatomical position, and all intended performance of the investigational valve as shown in the followings were achieved.<br>• No prosthetic valve - patient mismatch<br>• Mean pressure gradient < 20 mmHg or maximum aortic flow velocity < 3 m/s<br>• No ≥ moderate aortic valve regurgitation</td><td>VARC-2</td></tr>
<tr><td>Dry weight</td><td>The body fluid volume is proper, without excessive decrease in blood pressure during dialysis, and body weight with less burden on the cardiovascular system in a long-term basis.</td><td>Guidelines for evaluation and treatment of cardiovascular complication in hemodialysis patients</td></tr>
<tr><td>Dialysis conditions</td><td>The dialysis conditions are as shown below:<br>• Number of dialysis per week (times/week)<br>• Duration of dialysis (hours)<br>• Blood flow (mL)<br>• Quantity of dialysate flow (mL)<br>• Removal method (filtration or diffusion)<br>• Dialyzer membrane type and membrane area<br>• With or without High Performance Membrane (HPM) dialyzer</td><td>Guidelines for maintenance hemodialysis: Blood prescription</td></tr>
<tr><td>Embolism</td><td>Free blood clots or lesional substance in blood in the systemic circulation or pulmonary circulation.<br>All embolic events occurred under the circumstances with no infections immediately after perioperative period (at complete recovery from loss of consciousness by general anesthesia).<br>Embolic events in the peripheral vascular system are embolisms recorded as surgery, autopsy, or clinically, and symptoms associated with total or partial occlusion of the peripheral artery (except cerebral artery). Conscious patients with myocardial infarction should be excluded. Unless coronary artery embolism was caused by myocardial infarction is evident by surgery, autopsy, or clinical investigation, also patients with myocardial infarction after perioperative period should be excluded. If it was evident that an embolus consists of non-thrombotic substances (for example, arteriosclerosis, myxoma), it would be excluded.</td><td>STS</td></tr>
<tr><td>Endocarditis</td><td>When applicable to any one of the followings:<br>• Duke diagnostic criteria<br>• A histological or bacteriological test during re-operation reveals an abscess secondary to infection, paravalvular regurgitation and/or verruca<br>• An autopsy reveals an abscess related to the implanted valve and/or verruca</td><td>VARC-2</td></tr>
</table>

| Term | Definition | Reference/rationale |
|---|---|---|
| | <Duke diagnostic criteria><br>I. Clinical criteria<br>Meeting 2 major criteria, or 1 major criterion and 3 minor criteria, or 5 minor criteria.<br>(Major diagnostic criteria)<br>1. Positive blood culture for typical infective endocarditis organisms<br>A. Any one of the followings was found from 2 separate blood cultures<br>i. *Streptococcus viridans*, *Streptococcus bovis*, HACEK group<br>ii. *Staphylococcus aureus or Enterococcus* was detected, with no other infection focus<br>B. Positive blood culture corresponding persistent infective endocarditis defined as followings:<br>i. Two or more positive cultures from samples drawn ≥ 12 hours apart<br>ii. All 3 or a majority of 4 separate positive blood cultures (first and last sample drawn ≥ 1 hour apart)<br>2. Endocardial have been affected applicable to A or B below:<br>A. Echocardiogram positive for infective endocarditis with any one of the followings<br>i. Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation<br>ii. Abscess<br>iii. New partial dehiscence of prosthetic valve<br>B. New valve incompetence (deterioration of existing noise or change alone is not adequate)<br><br>(Minor diagnostic criteria)<br>1. Predisposition: Predisposing heart condition or intravenous drug use<br>2. Fever: ≥ 38.0°C<br>3. Vascular phenomena: Major vascular emboli, septic infarction, infective mycotic aneurysms, intracranial bleed, conjunctival hemorrhages, Janeway lesions<br>4. Immunologic phenomena: Glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor<br>5. Microbiological evidence: Positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with endocarditis<br>6. Echocardiographic findings: Consistent with endocarditis but do not meet a major criterion as noted above<br><br>II. Pathological criteria<br>Microorganism: Demonstrated by culture or histology in a vegetation or in a vegetation that has embolized, or in an intracardiac abscess: Pathologic lesions: Vegetation or intracardiac abscess present confirmed by histology showing active endocarditis. | |
| Enrolled subjects | Enrollment in this clinical trial should be completed by the document describing the patient's eligibility finally determined by case review. Enrollment in the continued access registry should be completed by the start of the study procedure (at the | |





| Term | Definition | Reference/rationale |
|---|---|---|
| | time point when an invasion such as an incision is made on the access site). | |
| Bailout subjects | Patients in whom deployment of the THV by balloon dilatation at a nominal volume was impossible for a medical reason will be regarded as bailout cases. | |
| Valve explants | Removal of the implanted investigational valve for any reason. (See "Re-operation") | STS/AATS |
| Length of post-procedural hospitalization | A period from the day of study procedure to hospital discharge. | |
| Study procedure | Study procedure refers to the procedure using the study device specified in the protocol for this clinical trial. The time of the start of the study procedure is the time after a subject's entering the operation room when invasion such as incision was made on the access site, and the time when closing the access site such as incision site was completed should be regarded as the end of study procedure. | |
| Infections | Known infections that require intravenous administration of antibiotics for reasons other than prophylactic use or prolonged hospitalization. | |
| Intent-to-treat (ITT) analysis set | Regardless of whether or not the study procedure was given, or whether or not the study device was implanted, the intent-to-treat (ITT) analysis set is defined as an analysis population consists of all subjects enrolled in this clinical trial. | |
| Past medical history | History of a disease, disorder, etc. that had developed before the start of the study procedure and resolved at the start of the study procedure. | |
| Mitral valve tissue damage or dysfunction | Damage to the mitral valve tissue (chorda tendineae, papillary muscles, or cusp) or dysfunction (limitation posed by the investigational valve) newly found during or after the study procedure in the angiogram or echocardiography findings. | VARC-2 |
| Mitral valve incompetence | A condition where the mitral valve does not close properly at systole, with blood regurgitation from the left ventricle to the left atrium, and the severity will be assessed in accordance with the followings:<br><Severity classification of mitral valve incompetence> | ASE |

| | Mild<br>1+ | Moderate<br>2+ | Moderate - Severe<br>3+ | Severe<br>4+ |
|---|---|---|---|---|
| Color flow jet | Transvalvular and small (< 4 cm² or < 10% of the left atrial area) | Transvalvular and moderate (4 - 6 cm² or < 10 - 30% of the left atrial area) | Transvalvular and large (> 6 cm² to < 8 cm² or > 30% to < 40% of the left atrial area), or aberrant reaching the 1st pulmonary vein | Transvalvular and large (≥ 8 cm² or ≥ 40% of the left atrial area), aberrant reaching the 2nd pulmonary vein |
| Pulmonary venous blood flow | Systole predominant | Diastole predominant | Entire diastole | Systolic regurgitation |
| Regurgitation volume (mL/beat) | < 30 | 30 - 44 | 45 - 59 | ≥ 60 |
| Regurgitation fraction (%) | < 30 | 30 - 39 | 40 - 49 | ≥ 50 |
| Effective regurgitant orifice area (cm²) | < 0.20 | 0.20 - 0.29 | 0.30 - 0.39 | ≥ 0.40 |
| Vena contracta width | < 0.5 cm | | ≥ 0.5 cm | |





| Term | Definition | Reference/rationale |
|---|---|---|
| mRS | A commonly used international scale as the prognosis rating scale for daily activities of patients with stroke.<br><br>0 — No symptoms at all<br>1 — No significant disability despite symptoms; able to carry out all usual duties and activities<br>2 — Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance<br>3 — Moderate disability; requiring some help, but able to walk without assistance<br>4 — Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance<br>5 — Severe disability; bedridden, incontinent and requiring constant nursing care and attention<br>6 — Dead<br>(see Appendix 2 "Modified Rankin Scale (mRS)") | |
| Myocardial Infarction | When meeting any one of the followings, it is defined as myocardial infarction.<br><br>• **Periprocedural myocardial infarction** (within 72 hours post-procedure)<br>When meeting both of the following criteria, it is regarded as periprocedural myocardial infarction.<br>○ Newly developed ischemic symptoms (chest pain, shortness of breath, etc.) or signs (ventricular arrhythmia, newly developed or worsened heart failure, new ST change, unstable hemodynamics, newly developed abnormal Q-wave ≥ 2 leads, new imaging information of normal myocardial loss, or regional wall abnormal motion).<br>○ CK-MB within 72 hours post-procedure > 5 times the upper range limit (URL), or troponin > 15 times.<br><br>• **Idiopathic myocardial infarction** (72 hours post-procedure)<br>When meeting any one of the following criteria, it is regarded as idiopathic myocardial infarction.<br>○ Elevation of CK-MB or troponin over the reference standard, together with at least one of the following findings:<br>• Symptoms of ischemia<br>• ECG changes indicative of new ischemia (ST-T changes, LBBB)<br>• Newly developed abnormal Q-wave at ≥ sequential 2 leads<br>• Imaging evidence of a new loss of viable myocardium or new wall motion abnormality.<br>○ Unexpected sudden death including cardiac arrest (developing symptoms primarily suggestive of myocardial ischemia, with new ST elevation or new LBBB, and/or death before blood sampling or development of myocardial biomarker in blood, with a newly developed clot by angiogram and autopsy.<br>○ Pathological findings of acute myocardial infarction | VARC-2 |
| NIHSS | Neurological severity scale for stroke developed by National Institutes of Health (NIH).<br>(see Appendix 1 "NIHSS") | NIH |





| Term | Definition | Reference/rationale |
|---|---|---|
| Non-structural dysfunction | Although abnormality is not of the prosthetic valve itself (namely the valve structure is normal), abnormality leading to stenosis regurgitation. Non-structural dysfunction includes pannus formation, proliferation of own tissues, engulfed suture, paravalvular regurgitation, inappropriate sizing or implantation position, residual leakage or obstruction after implantation of the valve, and clinically significant hemolytic anemia.<br>(see "Paravalvular regurgitation") | STS/AATS |
| NYHA classification of cardiac performance | Classification of cardiac performance developed by New York Heart Association, which classifies the severity of heart failure into 4 classes based on the subjective symptoms.<br><br><NYHA classification of cardiac performance><br><br>Class I — No limitations of physical activities. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or angina pectoris.<br>Class II — Slight limitation of physical activity. Asymptomatic at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina pectoris.<br>Class III — Marked limitation of physical activity. Asymptomatic at rest. Less than ordinary physical activity leads to fatigue, palpitations, dyspnea, or angina pectoris.<br>Class IV — Inability to carry on any physical activity without discomfort. Symptoms of heart failure or angina pectoris present at rest. These symptoms may be exacerbated by a slight exertion. | NYHA |
| Paravalvular regurgitation | All blood leakages around the prosthetic valve associated with the gap between the prosthetic valve and native annulus.<br><br>Paravalvular regurgitation can be classified as follows:<br><br>Total regurgitation: Moderate to severe paravalvular dysfunction clearly observed by echocardiography.<br>Mild regurgitation: Paravalvular regurgitation classified as aortic valve regurgitation < 3+ and not requiring surgical intervention.<br>Severe regurgitation: Aortic valve regurgitation ≥ 3+ and requiring surgical intervention.<br><br>(also see "Non-structural dysfunction) | STS/AATS |
| Pre-procedural complication | Defined as any complication developed before the start of the study procedure and the symptoms sustained or under treatment at the start of the study procedure. | |

<table>
<tr><th>Term</th><th>Definition</th><th>Reference/rationale</th></tr>
<tr><td>Prosthesis-patient mismatch (PPM)</td><td>Prosthesis-patient mismatch (PPM) is an index to show a relationship between the implanted prosthetic valve and cardiac output originally required for the subject. When the aortic flow velocity coefficient by continuous wave Doppler method is normal (> 0.35), but EOAi ≤ 0.85 (BMI < 30), it is regarded as hemodynamically significant prosthesis-patient mismatch.<br><table><tr><th></th><th>Not significant</th><th>Moderate</th><th>Severe</th></tr><tr><td>EOAi ($cm^2/m^2$) [BMI < 30 $kg/cm^2$]</td><td>> 0.85</td><td>0.85 - 0.65</td><td>< 0.65</td></tr><tr><td>EOAi ($cm^2/m^2$) [BMI ≥ 30 $kg/cm^2$]</td><td>> 0.70</td><td>0.90 - 0.60</td><td>< 0.60</td></tr></table></td><td>VARC-2</td></tr>
<tr><td>Re-hospitalization</td><td>Re-hospitalized due to AS symptoms and/or post-procedural complication.<br><br>If the post-procedural hospital stay exceeds 30 days, in-hospital Day 31 is statistically regarded as re-hospitalization.</td><td></td></tr>
<tr><td>Re-intervention</td><td>All interventions including repair, correction, or replacement of the already operated valve.</td><td>STS/AATS</td></tr>
<tr><td>Stroke/transient ischemic attack</td><td><Stroke/transient ischemic attack diagnostic criteria><br>Acute onset of a local or general neurological disorder, with at least one of the followings: changes in the conscious level, hemiplegia, hemiparesis, numbness, sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, and other neurological signs or symptoms consistent with stroke.<br><br>Stroke:<br>Local or general neurological disorder sustains ≥ 24 hours, or even < 24 hours new hemorrhage or infarction is found by head neuroimaging, or a neurological disorder resulted in death.<br><br>Transient ischemic attack:<br>Local or general neurological disorder sustains < 24 hours, with no new hemorrhage or infarction by head neuroimaging.<br><br>As for clinical findings, the absence of causes other than stroke that can be easily identified (brain tumor, trauma, infection, hypoglycemia, peripheral lesion, influence of drug, etc.) must have been determined by a neurologist or together with a neurologist*. Definitive diagnosis should be made by at least one of the followings:<br><br>• Diagnosis by a neurologist or neurosurgeon<br>• Head neuroimaging (CT scan or brain MRI); however stroke may be diagnosed only by the clinical findings<br><br>* Do not report non-local encephalopathy as stroke, unless findings of cerebral infarction are present based on the head neuroimaging (CT scan or brain MRI).<br><br><Stroke classification><br>Ischemic: Acute angiopathy at the local brain, spinal cord, or retina associated with infarction in the central nervous system tissues<br>Hemorrhagic: Acute angiopathy at the local or general brain or spinal cord associated with hemorrhage in the cerebral parenchyma, cerebral ventricle, or</td><td>VARC-2</td></tr>
</table>





<table>
<tr><th>Term</th><th>Definition</th><th>Reference/rationale</th></tr>
<tr><td></td><td>subarachnoid<br><br>If the information is inadequate for determining ischemic or hemorrhagic, classify as cause unknown.<br><br><Definition of stroke><br>Stroke is classified into disabling or nondisabling.<br><br>• Disabling stroke<br>At 90 days after the onset of a stroke, mRS ≥ 2, and exacerbation ≥ 1 in the mRS from before the onset.<br><br>• Non-disabling stroke<br>At 90 days after the onset of a stroke, mRS < 2, and no exacerbation ≥ 1 in the mRS from before the onset.</td><td></td></tr>
<tr><td>Structural valve deterioration</td><td>All changes in the functions of the implanted valve resulted from abnormality specific to the valve that may lead to stenosis or regurgitation (exacerbation ≥ 1 of NYHA classification of cardiac performance).<br><br>Structural valve deterioration includes dysfunction or degradation of the implanted valve, while infection or thrombosis confirmed by re-operation, autopsy, or laboratory tests is not included. Structural deterioration means substantial change in the valve, including wear, damage, calcification, rupture of the cusp, and fraying of the joining thread for the components (e.g.: cusp).</td><td>STS/AATS</td></tr>
<tr><td>Valve thrombosis</td><td>All thrombi adhered to the implanted valve or around the valve that obstruct part of the blood flow paths, or interfere with valve functions, or are large enough to be treated. Valve-related thrombus observed at autopsy of a death case that was assessed as unrelated to the study device will not be regarded as valve thrombosis.</td><td>VARC-2</td></tr>
<tr><td>Unplanned use of artificial heart-lung machines</td><td>Cases for which artificial heart-lung machines were used unplanned for circulatory assistance during study procedure.</td><td>VARC-2</td></tr>
<tr><td>Valve implant analysis set</td><td>The subject population consisting for all subjects in whom the THV was implanted, and when the subject exited the operation room the implanted THV was maintained is defined as valve implant (VI) analysis set. Subjects for whom the investigational valve was not implanted, including subjects switching to surgery, and TAVI bioprosthetic valve other than the investigational valve was implanted, will not be included in the VI analysis set. As for subjects who received a valve-in-valve procedure, cases with additional investigational valve implantation will be included in the VI analysis set, while cases with additional TAVI bioprosthetic valve other than the investigational valve will be excluded from the VI analysis set.</td><td></td></tr>
<tr><td>Valve-in-valve procedure</td><td>Implantation of a new prosthetic valve in the already implanted prosthetic valve during or after the study procedure due to inappropriate implantation position and/or valve function.</td><td>VARC-2</td></tr>
<tr><td>Ventricular septal perforation</td><td>New ventricular septal perforation newly found during or after the study procedure by angiogram or echocardiography findings.</td><td>VARC-2</td></tr>
</table>





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