A Feasibility Study to Assess Safety and Effectiveness of the Transfemoral JenaValve Pericardial TAVR System in the Treatment of Patients with Symptomatic Severe Aortic Stenosis (AS)

THE ALIGN-AS EFS TRIAL: JenaValve Pericardial TAVR Aortic Stenosis Study

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Protocol Synopsis

Title	An early feasibility study to assess safety and effectiveness of the transfemoral JenaValve Pericardial TAVR System in the treatment of patients with symptomatic severe aortic stenosis (AS)
Study Objective	The objective of this study is to evaluate the safety and effectiveness of the transfemoral JenaValve Pericardial TAVR System in a patient population with symptomatic severe AS requiring replacement of their native aortic valve that are at high risk for open surgical aortic valve replacement (SAVR).
Study Design	Prospective, multicenter, single arm feasibility study
Study Devices	The JenaValve Pericardial TAVR System contains the following subcomponents: a prosthetic transcatheter porcine pericardial aortic valve, 19Fr introducer sheath system, transfemoral delivery catheter, and loading tool.
Indications for Use	The JenaValve Pericardial TAVR System is intended for use in patients with symptomatic, severe aortic stenosis (AS) who are at high risk for surgical aortic valve replacement (SAVR) and who meet all of the inclusion criteria outlined in this clinical protocol. The JenaValve Pericardial TAVR System is contraindicated for use in patients who have any of the exclusion criteria outlined in this clinical protocol.
Number of Sites	A maximum of 10 centers located in the United States; maximum of 8 centers in Germany for a total of maximum of 12 centers in Europe, maximum of 3 centers in NZ
Number of Subjects	A maximum of 40 subjects will be enrolled in the US, A maximum of 30 subjects in the Netherlands, A maximum of 30 subjects in Germany, and a maximum of 30 subjects in New Zealand
Population	The study population will consist of subjects with severe symptomatic AS who are at high risk for SAVR and have a predicted risk of operative mortality ≥8% at 30 days as assessed by the local heart team consisting of a minimum of 2 physicians (at least one interventional cardiologist and one cardiac surgeon).
Inclusion Criteria	1. Adult patients with severe degenerative native AS; as assessed by either resting or stress echocardiography: - mean pressure gradient > 40 mmHg or peak jet velocity > 4.0 m/s; AND - aortic valve area $\leq$ 1.0 cm^2; OR - indexed aortic valve area $\leq$ 0.6 cm^2/m^2 2. Patient symptomatic according to NYHA functional class II or higher 3. Patient at high risk for SAVR (STS ≥ 8% or if STS < 8%, a documented heart team agreement determines that significant co-morbidities are

	not captured on STS), and heart team agrees that patient can undergo SAVR for "bail out"/to address unfavorable circumstances if necessary 4. Patient has suitable anatomy to accommodate the insertion and delivery of the JenaValve delivery system 5. Patient or the patient's legal representative has provided written informed consent 6. Patient or the patient's legal representative agrees to comply with all required post-procedure follow-up visits
Exclusion Criteria	1. Congenital uni- or bicuspid aortic valve morphology 2. Previous prosthetic aortic valve (bioprosthesis or mechanical) implant 3. Mitral regurgitation > moderate 4. Clinically significant coronary artery disease (CAD) requiring revascularization within 30 days prior to index procedure, or planned CAD revascularization procedure within 12 months after index procedure 5. Echocardiographic evidence of left cardiac thrombus 6. Endocarditis or other active infection 7. Hypertrophic cardiomyopathy with or without obstruction 8. Severe pulmonary hypertension (systolic PA pressure > 80 mmHg) or severe RV dysfunction (RV fractional area change <35%, or TAPSE < 16 mm, or tissue Doppler S' <10) 9. Very severely reduced left ventricular ejection fraction (LVEF <20%) 10. Aortic annular diameter of < 21 mm or > 27 mm (assessed by Multi-detector CT measurement) 11. Aortic annulus angulation > 60° (assessed by Multi-detector CT measurement) 12. Straight length of ascending aorta of < 55 mm 13. Significant disease of ascending aorta, including ascending aortic aneurysm (defined as maximal luminal diameter of 50 mm or greater) or atheroma (including if thick [>5 mm], protruding or ulcerated) 14. Need for urgent or emergent TAVR procedure for any reason 15. Cardiogenic shock or hemodynamic instability requiring inotropic support or ventricular assist device 16. Myocardial infarction < 30 days prior to index procedure 17. Cerebrovascular event (TIA, stroke) < 180 days prior to index procedure 18. Severe renal insufficiency (GFR < 30 ml/min), OR renal disease requiring renal replacement therapy 19. Blood dyscrasias as defined: leukopenia (WBC < 3000/mm^3), or thrombocytopenia (platelets < 90,000/µl) or anemia (Men: Hgb < 8.1 g/dl; Women: Hgb < 7.4 g/dl) 20. Active peptic ulcer or upper gastrointestinal bleeding < 90 days prior to index procedure

	21. Known hypersensitivity or contraindication to aspirin, heparin, ticlopidine or clopidogrel, nitinol, tantalum or allergy to contrast agents that cannot be premedicated 22. Contraindication to intraoperative transesophageal echocardiography and/ or Multi-Detector CT (MDCT) scan 23. Estimated life-expectancy of < 24 months 24. Patient is enrolled in another investigational medical device or drug study, which has not completed the required primary endpoint follow-up. *(Note: Patients involved in a long-term surveillance phase of another study are eligible for enrollment in this study)* 25. Other medical, social, or psychological conditions that in the opinion of an Investigator precludes the patient from providing appropriate informed consent 26. Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up assessments). 27. Unable to comply with follow-up requirements
Study Endpoints and Analyses	Study endpoints are defined according to the standardized endpoint definitions for transcatheter aortic valve implantation as outlined in The Valve Academic Research Consortium-2 consensus document (i.e., VARC-2). *Primary Safety Endpoint* All-cause Mortality at 30 days *Performance Endpoints* • Technical Success at exit from OR, hybrid room or cath lab post-index procedure (VARC-2) • Procedural Success at 1-month (VARC-2), consisting of: • Device Success at 1-month, 6-months, 1-year and annually thereafter for up to 5 years • Individual Patient Success at 1-year and annually thereafter up to 5 years • NYHA functional classification at discharge, 1-month, 6-months, 1-year, and annually thereafter for 5 years • 6-minute walk test at 6 months, 1 year and annually thereafter for 5 years • Kansas City Cardiomyopathy Questionnaire at 1 year and annually thereafter for 5 years • Clinically acceptable hemodynamic performance and function as confirmed by Core Lab evaluation of echocardiography for the following parameters at discharge, 1-month, 6-months, 1-year, and annually thereafter for 5 years:

Schedule of Tests:

Pre-procedural echocardiography (TEE or TTE) and a baseline multi-detector CT scan with Core Lab assessment are used to determine anatomical eligibility for enrollment. Following ethics committee/IRB approval and patient written informed consent, the patient will be screened for eligibility by heart teams. Final eligibility determination is made by an Independent Screening Committee evaluation of site screening records and Core Lab measurements/assessments. After the procedure, enrolled patients are to be followed immediately post- procedure, at hospital discharge, and then at 1 month, 6 months, 1 year; and annually thereafter for 5 years, listed in Schedule of Assessments Table below:

Schedule of Assessments:	**Screening/ Baseline**	**Procedure (Day 0)**	**Pre-Discharge**	**1 Month**	**6 Months**	**1- to 5-years**
Medical History including consent	x					
STS Score	x					
Targeted Physical Exam[†]	x		x	x	x	x
Laboratory Tests[‡]	x		x	x	x	x
Pregnancy Test[α]	x					

Multi-detector CT Imaging [¥]	x					
12 lead ECG / Rhythm Strip	x		x	x	x	x
Echocardiography (TTE or TEE) [¥]	x	x	x	x	x	x
NYHA Classification	x		x	x	x	x
6 minute walk test (6MWT)	x				x	x
KCCQ	x					x
Modified Rankin Scale & Mini Mental State Exam (MMSE) [§]	x		x	x	x	x
Cardiovascular Medications	x	x	x	x	x	x
Adverse Events		x	x	x	x	x

[†] Physical exam includes overall health and physical assessment and vital signs.

[‡] Labs include a complete blood count (CBC): WBC with differential, RBC with HCT and Hb, platelet count, coagulation panel (PT, PTT and an INR for subjects on vitamin-K antagonist), creatinine, urine or serum albumin, C-reactive protein, plasma-free Hb, serum LDH or haptoglobin and cardiac biomarkers (troponin I or T or CK/CK-MB) will be assessed at baseline, discharge, 1 month, 6 months, 1 year and annually thereafter for 5 years.

[α] Only for females of child bearing potential and performed within 72 hours prior to index procedure.

[¥] Imaging procedures performed within 1 year prior to index procedure may be used for baseline, unless otherwise indicated.

[§] Modified Rankin Scale is performed for each patient at baseline and at each follow-up interval thereafter until study completion. MMSE is performed at Screening/Baseline only unless subject experiences a stroke.

Follow-up windows: ±7 days (1-month visit); ±30 days (6-month visit); ±2 months (1- to 5-Year visits)**.** Screening tests with the exception of imaging procedures should be performed within 60 days of index procedure.

1.0 INTRODUCTION

The objective of this study is to evaluate the safety and effectiveness of the transfemoral JenaValve Pericardial TAVR System in treating subjects with symptomatic severe aortic stenosis requiring replacement of their native aortic valve; who are at high risk for open surgical aortic valve replacement (SAVR), by using a minimally invasive transcatheter aortic valve replacement (TAVR) procedure. The study protocol will ensure consistency in performing the procedure, patient management, and results of the procedure. The results of this feasibility study shall be used to design a pivotal trial to support a PMA application for approval of the JenaValve Pericardial TAVR System for treatment of aortic stenosis.

1.1 Background on Aortic Stenosis and TAVR

Degenerative aortic valve stenosis is the most common heart valve problem in adults in western industrialised nations (Iung, et al., 2003). Prevalence grows continuously as age increases such that, in view of growing life expectancy and demographic development, patients in their eighth and ninth decades of life are also particularly affected – representing a challenge for therapeutic management (Lindroos, Kupari, Heikkila, & Tilvis, 1993). Patients with aortic valve stenosis are asymptomatic until late in the course of disease. However, as soon as the first symptoms such as angina pectoris, syncope and dyspnoea occur, the prognosis is poor (Vahanian, et al., 2002). Clinical studies report a mortality rate of 25% in the first year and 50% in the second year after the onset of symptoms, despite drug-based therapy (Frank, Johnson, & Ross, 1973).

Open surgical aortic valve replacement (SAVR) is the treatment of choice. Patients treated benefit from relief of symptoms and significant improvement in long-term survival (Schwarz, et al., 1982). The procedure is carried out under general anaesthesia via sternotomy and the use of extracorporeal circulation. Despite improved operating techniques and intensive care support afterwards, the operation represents a high-risk procedure in patients over the age of 75 with multiple co-morbidities (Bernard, et al., 1992). Concomitant diseases such as renal failure, pulmonary hypertension, heart failure or previous cardiac surgery can lead to a significant increase in peri-operative morbidity and mortality (Iung, et al., 2003) (Roques, et al., 1999) (Vaquette, et al., 2005). In view of the growing proportion of this patient group in the overall population, there is a growing demand for alternative methods for lesser invasive and potentially safer aortic heart valve replacement.

1.2 Background on Transcatheter Aortic Valve Replacement (TAVR)

In this context, transcatheter aortic valve replacement (TAVR) was developed as a treatment option that enables implantation of a biological valve in a minimally invasive procedure without the need for sternotomy and extracorporeal circulatory support. Since the first percutaneous transluminal implantation of an aortic valve was carried out in humans in 2002, the procedure has been performed on more than 50 000 patients worldwide. (Piazza, et al., 2008) There are essentially two key access pathways via which the aortic valve prosthesis can be implanted: via antegrade access, a left lateral mini-thoracotomy is performed and the apex of the left ventricle is punctured with a cannula through which a stiff guidewire is inserted. A delivery catheter which encloses the valve prosthesis is inserted in over the wire technique and advanced through the left ventricle into the ascending aorta (transapical TAVR). Alternatively, the retrograde technique allows the implantation of the aortic valve prosthesis via transarterial access following puncture

of the iliofemoral artery. The delivery catheter which encloses the aortic valve prosthesis is advanced retrograde through the aorta into the aortic root (transfemoral TAVR). Patients with contraindications for transapical or transfemoral access can potentially be treated via subclavian or direct aortic access (Bauernschmitt, et al., 2009).

Since the first implantation in 2002 a remarkable number of case studies, clinical trials and registries in TAVR were performed. To date, results from multiple randomized clinical trials comparing TAVR and SAVR are available in various risk levels. In the PARTNER trial, safety and effectiveness of the Edwards SAPIEN transcatheter aortic valve was evaluated. Cohort A compared TAVR with SAVR in patients with high operative risk. Cohort B compared TAVR to medical treatment in inoperable patients. Results for Cohort A were published in 2011 showing that TAVR is non-inferior to SAVR with respect to all-cause mortality at one year. (Smith, et al., 2011) Results for Cohort B were published in 2010 already showing that TAVR significantly reduced all-cause mortality by nearly 50%, thus being superior to medical treatment in inoperable patients. (Leon, et al., 2010) In the CoreValve extreme risk trial, patients with symptomatic AS at extreme operative risk were randomized to either SAVR or TAVR using the CoreValve® (Medtronic, MN, USA). The rate of all-cause mortality at 12 months was significantly lower in the TAVR group when compared to the SAVR group. Current guidelines state that TAVR is an acceptable alternative to surgical AVR in selected operable high-risk patients, and that the benefit from TAVR greatly exceeds the risk in inoperable patients (Holmes, et al., 2012). Based on these convincing results TAVR has emerged as an accepted treatment option for high-risk patients with severe aortic stenosis. The SAPIEN (P100041/P110021), SAPIEN XT (P130009), SAPIEN 3 (P140031), CoreValve and CoreValve Evolut R (P130021), and Lotus Edge (P180029) TAVR devices have obtained US FDA approval for treatment of patients with severe aortic stenosis who are at extreme or high risk for SAVR. Extended approvals for intermediate risk patients are available for some devices.

According to a recent European registry including more than 4500 patients, 16.4% of all TAVR procedures were performed via the TA access route (Di Mario, Eltchaninoff, Moat, Goicolea, & et al., 2013). Besides the JenaValve TA TAVR system, which consists of a porcine aortic root mounted on a self-expandable Nitinol stent and the Cathlete™ delivery system, four TA TAVR devices received CE mark: the SAPIEN XT/SAPIEN 3 (Edwards Lifesciences, CA, USA), Engager (Medtronic, MN, USA) and ACURATE TA (Symetis SA, Switzerland). In contrast to the JenaValve System, which can be deployed without rapid pacing, all four other TA systems rely on rapid pacing during deployment to minimize left ventricular output and stabilize the position of the valve prosthesis during deployment. Of all devices mentioned above, the SAPIEN XT and SAPIEN 3 are the only balloon-expandable valve prostheses.

The SAPIEN™/SAPIEN 3 as well as the ACURATE TA bioprosthesis anchor within the aortic root through active or passive expansion of the stent by transferring the force onto the wall of the aortic annulus or the ascending aorta. The prostheses are inserted, positioned and deployed under fluoroscopic control in order to avoid malpositioning with the risk of antegrade (into the aorta) or retrograde (into the left ventricle) embolization of the valve or obstructing the coronary ostia. The precise positioning and correct placement of the valve prosthesis is a demanding and crucial element in all catheter-based valve implantation techniques.

1.3 JenaValve Device Concept

JenaValve has developed a new system for transcatheter aortic valve replacement that differs from other available systems. The JenaValve Pericardial TAVR System is designed to allow a controlled valve release and deployment during the entire implantation procedure under beating heart conditions. The JenaValve Pericardial Transcatheter Heart Valve (THV) prosthesis includes three positioning locators which are released in a first step during implantation [redacted] After introducing the system via transapical or transfemoral access, the positioning locators are released under fluoroscopic control. By gently advancing (TF approach) or retracting (TA approach) the respective delivery system towards the aortic root, the locators are positioned in native aortic valve cusps. [redacted] After correct true anatomical positioning, the prosthesis is released and deployed stepwise. Once the valve is unfolded by the self-expanding mechanism of the Nitinol stent, the native aortic valve cusps are fixed in between the locators and the rail (see **Figure 1**), thus defining correct height and position of the valve prosthesis.

1.4 JenaValve Device Preclinical Testing

[redacted] Thus, frequently used large animal models such as ovine or swine model have limitations to fully evaluate TAVR devices but nevertheless can provide valuable information about device performance, deliverability and valve functionality. JenaValve conducted acute and chronic preclinical animal studies using the ovine model. Acute animal studies have demonstrated the feasibility of successful delivery and implantation of the JenaValve Pericardial TAVR System with very good hemodynamic valve performance post procedure. Results of chronic GLP studies revealed excellent long-term macroscopic/microscopic outcomes with no signs of valve degeneration or dislocation. Valve performance was evaluated by echocardiography at predefined time points throughout the studies and demonstrated durable long term effectiveness of the valve.

The positive in-vitro and in-vivo results with the JenaValve Pericardial TAVR System are a substantial base to justify the conduct of a clinical feasibility study with the JenaValve Pericardial TAVR System in patients who suffer from severe aortic stenosis and who are not considered suitable candidates to undergo surgical aortic valve replacement.

1.5 Prior Clinical Experience with JenaValve Device

The JenaValve system was CE-Marked for treatment of aortic stenosis (AS) on September 30, 2011, based on a multicenter, prospective, single arm trial conducted at seven (7) centers in Germany that enrolled 73 patients. This trial showed the JenaValve system was safe and effective in the treatment of severe AS in patients at high risk for surgery [Treede, et al., 2012]. A subsequent indication for treatment of aortic regurgitation (AR) in high surgical risk patients was granted CE Mark on September 16, 2013. [Seiffert, et al, 2014] A post-approval clinical registry, (the JUPITER Registry, NCT01598844) was conducted in Europe to continue the assessment of product performance in 180 patients with severe AS. The interim results of the JUPITER study

were presented by Wendler at EuroPCR, Paris, France on May 20-23, 2014. One-year results have been published (Silaschi et al. 2017). This study is now completed.

[redacted]

1.6 Conclusion

The positive in-vitro and in-vivo results with the JenaValve Pericardial TAVR System are a substantial base to justify the conduct of an early feasibility clinical study with the JenaValve Pericardial TAVR System in patients who suffer from severe aortic stenosis and who are not considered suitable candidates to undergo surgical aortic valve replacement. Based on the encouraging initial experiences, the Sponsor believes that a multi-center, prospective, feasibility study of a TAVR transfemoral approach for treatment of aortic stenosis is warranted.

2.0 DEVICE DESCRIPTION

This study is investigating the JenaValve Pericardial TAVR System when used to perform transcatheter aortic valve repair (TAVR) for treatment of severe aortic stenosis. The JenaValve Pericardial TAVR System consists of three (3) major components:

- JenaValve Pericardial Transcatheter Heart Valve (THV)
- JenaValve Pericardial Transfemoral (TF) Delivery Systems
- JenaValve Pericardial Transfemoral (TF) Loading Tools

Intended Use: The JenaValve Pericardial TAVR System is intended for use in patients with symptomatic, severe aortic stenosis (AS) who are at high risk for surgical aortic valve replacement (SAVR) and who meet all of the inclusion criteria outlined in this clinical protocol.

The JenaValve Pericardial TAVR System is contraindicated for use in patients who have any of the exclusion criteria outlined in this clinical protocol.

2.1 JenaValve Pericardial Transcatheter Heart Valve (THV)

The JenaValve Pericardial Transcatheter Heart Valve (**Figure 1**) is constructed from porcine pericardium that is attached to a self-expanding Nitinol frame with polyester suture. The frame has a crown design that can collapse with the valve to be implanted using the JenaValve Transfemoral (TF) Delivery System.

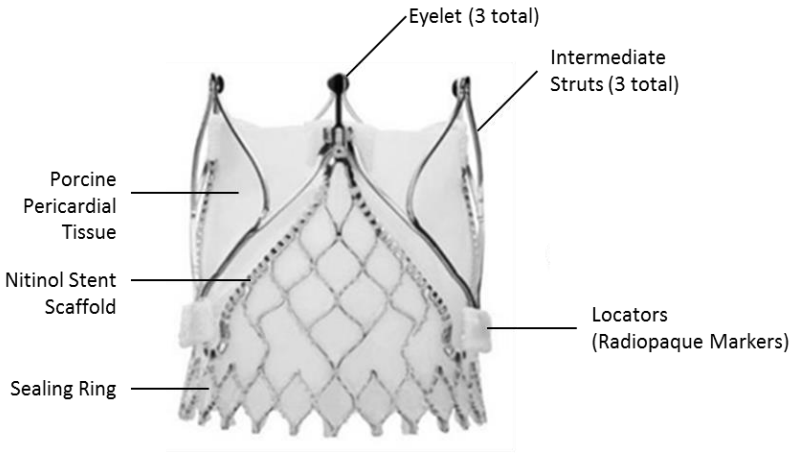

Figure 1: JenaValve Pericardial THV

2.2 JenaValve Pericardial Transfemoral (TF) Delivery System

The JenaValve Pericardial Delivery Systems is designed to allow for a transfemoral approach using the JenaValve Pericardial Transfemoral (TF) introducer Sheath and its compatible Delivery Catheter. The delivery system is designed to implant the JenaValve THV using percutaneous access.

2.2.1 JenaValve Coronatix™ Transfemoral (TF) Delivery Catheter & Introducer Sheath

The JenaValve Coronatix™ Delivery Catheter delivers the THV transfemorally through the JenaValve Pre-Shaped 19Fr Introducer Sheath. [redacted]. After Delivery Catheter introduction and THV/Locator positioning, a safety clip placed on the catheter handle is removed to permit push-activated deployment of the THV inflow segment (Sealing Ring), followed by secondary push-activated deployment of the THV outflow segment (Eyelets). After deployment, the Delivery Catheter is retracted into the Introducer Sheath and removed. The Delivery Catheter is sterilized by ethylene oxide gas and is for single use only.

[redacted]

The JenaValve Pericardial THV is crimped/loaded into the main delivery system at the time of the procedure using a dedicated loading tool. [redacted]

[redacted] Once position is confirmed the pre-shaped sheath is retracted proximally to expose the JenaValve Pericardial THV in the ascending aorta. At this point, the locators are exposed and "open" for cusp/positioning placement.

The JenaValve Pericardial THV is deployed via the main delivery system. Upon confirmation of the correct locator position, the most proximal delivery handle is used to deploy the THV. Following THV deployment, the catheter is slowly withdrawn from the THV and brought into the pre-shaped sheath, and the entire assembly is removed from the patient as a unit.

2.3 JenaValve Pericardial Transfemoral (TF) Loading Tools

JenaValve loading tools are available for the Transfemoral (TF) delivery system. The TF loading tool enables crimping and loading the THV into the delivery system. This is accomplished prior to insertion of the JenaValve Pericardial TAVR System into the body.

The Loading Tool consists of a Core which comes in 3 different sizes to accompany each valve size (23, 25 and 27), and a Loading Tube, Cone and Wheel which are not size-dependent. The tool is ethylene oxide-sterilized and for single use only.

2.4 Product Identification

Product identification is ensured for both the JenaValve Pericardial Transcatheter Heart Valve and the Delivery System. The THV can be identified by means of a model number and serial number. The delivery system components (introducer system, delivery catheter, and loading tool) are identified by lot numbers. See **Table 1** below for a list of Model numbers:

Table 1: JenaValve Transfemoral Pericardial TAVR System Model Numbers

Product Name	**Size 23 System**	**Size 25 System**	**Size 27 System**
JenaValve Everdur™ Pericardial Transcatheter Heart Valve	JV-2000-PY23	JV-2000-PY25	JV-2000-PY27
JenaValve Introducer Sheath System	INTR000001		
JenaValve Coronatix™ Transfemoral Delivery Catheter	CATH23TF01	CATH25TF01	CATH27TF01
JenaValve Transfemoral Loading Tools	LOAD23TF01	LOAD25TF01	LOAD27TF01

*One complete system includes one (1) of each of system components listed in Table 1.

3.0 STUDY OBJECTIVE

The objective of this study is to evaluate the safety and effectiveness of the transfemoral JenaValve Pericardial TAVR System in treating subjects with symptomatic severe aortic stenosis requiring replacement of their native aortic valve who are at high risk for open surgical aortic valve replacement (SAVR), using a minimally invasive transcatheter aortic valve replacement (TAVR) procedure. The

study protocol will ensure consistency in patient enrollment, procedural conduct, patient follow-up, data management, and results reporting. Results obtained in this feasibility study and investigational plan are intended to support the design and initiation of a pivotal trial to support a future PMA application for approval of the JenaValve Pericardial TAVR System for treatment of aortic stenosis.

4.0 STUDY ENDPOINTS/OTHER DATA COLLECTION

4.1 Primary Endpoint

The primary endpoint of the study is defined as All-Cause Mortality within the first 30 days post index procedure as adjudicated by the Clinical Events Committee/Data Monitoring Committee (CEC/DMC).

Study endpoints are defined according to the standardized endpoint definitions for transcatheter aortic valve implantation as outlined in The Valve Academic Research Consortium-2 consensus document (i.e., VARC-2).

4.2 Performance Endpoints

Performance endpoints are defined as below and measured at time points specific to each endpoint:

1. Technical Success at exit from OR, hybrid room or cath lab post-index procedure:
   - Absence of procedure mortality; *and*
   - Successful access, delivery and retrieval of transcatheter delivery system; *and*
   - Deployment and correct positioning of a single intended THV; *and*
   - Freedom from re-intervention related to the device or access

2. Procedural Success at 1-month (VARC-2), consisting of:
   - Device success at 30 days; *and*
   - No device- or procedure-related serious adverse events

3. Device Success at 1-month, 6-months, 1-year and annually thereafter for up to 5 years, consisting of:
   - Absence of procedure mortality; and
   - Correct position of a single prosthetic heart valve in the proper anatomic location
   - Intended performance of the prosthetic heart valve:
     - mean aortic valve gradient <20 mmHg *or* peak velocity <3 m/s; *and*
     - no moderate or severe prosthetic valve regurgitation

4. Individual Patient Success at 1-year and annually thereafter for up to 5 years, consisting of:
   - Device and Procedural Success (as defined above); and,
   - No re-hospitalizations or re-interventions for the underlying condition (e.g., aortic stenosis)
   - Improvement vs. baseline in symptoms (e.g., NYHA Class improvement >1 from baseline, or NYHA Class < III or IV)
   - Improvement vs. baseline in functional status (e.g., 6MWT improvement > 50 feet from baseline)

- Improvement vs. baseline in Quality of Life (QoL) (e.g., KCCQ improvement > 10 from baseline)

5. NYHA functional classification at discharge, 1-month, 6-months, 1-year, and annually thereafter for 5 years
6. 6-minute walk test at 6-months, 1 year and annually thereafter for 5 years
7. Kansas City Cardiomyopathy Questionnaire at 1 year and annually thereafter for 5 years
8. Clinically acceptable hemodynamic performance and function as confirmed by Core Lab evaluation of echocardiography for the following parameters at discharge, 1-month, 6-months, 1-year, and annually thereafter for 5 years:

4.3 Additional Analyses

4.3.1 Safety

The incidence of the following as determined by the Clinical Events Committee will be assessed at 1-month, 6-months, 1-year, and annually thereafter for 5 years:

A. Mortality
B. Myocardial Infarction
C. Neurological Complications
D. Bleeding Complications
   - Life-threatening or disabling (including fatal)
   - Major bleeding
   - Minor bleeding
E. Acute Kidney Injury (AKIN classification as Stage 1, Stage 2, or Stage 3, ≤7 days post-index procedure)
F. Vascular Complications
   - Minor
   - Major
   - Percutaneous device closure failure
G. Conduction Disturbances and Arrhythmias
H. Other TAVR-Related Complications

4.3.2 Other Data

Blood laboratory data includes complete blood count (CBC): WBC with differential, RBC with HCT and Hb, platelet count, coagulation panel (PT, PTT and an INR for subjects on vitamin-K antagonist), creatinine, urine or serum albumin, C-reactive protein, plasma-free Hb, serum LDH or haptoglobin and cardiac biomarkers (troponin I or T or CK/CK-MB) will be assessed at baseline, discharge, 1 month, 6 months, 1 year and annually thereafter for 5 years.

5.0 STUDY DESIGN

This is a prospective, multicenter, single-arm, feasibility study evaluating the safety and effectiveness of transcatheter aortic valve replacement utilizing the JenaValve Pericardial TAVR System for the treatment of aortic stenosis.

A maximum of 40 subjects will be enrolled in the US, a maximum of 30 subjects in the Netherlands, a maximum of 30 subjects in Germany, and a maximum of 30 subjects in New Zealand. A maximum of 10 centers in the United States, 8 centers in Germany for a maximum of 12 centers in Europe, and a maximum of 3 centers in New Zealand will participate in the study. The duration of the study is estimated at approximately 72 months total, for the period spanning enrollment (estimated at approximately 12 months) through completion of 2 year follow up in Germany, The Netherlands, and New Zealand and through 5 year follow-up in the United States.

[redacted] Other data collected from this study will also be considered in the development of the TAVR treatment for aortic stenosis.

6.0 STATISTICAL METHODS

6.1 General

Descriptive summaries will be the basis of study reports to generate an overall summary of the safety and effectiveness of the transcatheter aortic valve replacement utilizing the JenaValve Pericardial TAVR System for the treatment of aortic stenosis. Continuous outcome variables will be analyzed as means and standard deviations with 95% confidence intervals, as well as medians and ranges. For categorical outcome variables, relative frequencies will be determined. Descriptive tables will be produced for baseline characteristics including demographics, medical history, operative characteristics, and procedural outcomes, adverse events, physical exams, laboratory assessments, and hemodynamic variables.

6.1.1 Analysis of Endpoints

Exact binomial confidence interval will be provided for all endpoints measured within the first 30 days. Supplemental Kaplan-Meier event rates (95% CI) will be presented for time-to event outcomes at 30 days, 180 days, 1 year, and annually thereafter for 5 years. Time is calculated from index procedure to first event. Subjects who did not experience an event will be censored to the most recent follow up visit or withdrawal date.

The clinical outcomes measured by the NYHA, 6MWT, and KCCQ, are treated as continuous outcomes. The raw value and change from baseline at each time point will be analysed by repeated measures methodology. Only actual data will be used in this analysis. Note that for patients who are unable to perform the 6MWT, due to a medical reason will be considered to have walked an actual distance of zero.

6.1.2 Other

Reasonable efforts will be made to obtain complete data for all subjects; however, missing observations may occur due to subjects lost to follow-up or noncompliance with required assessments. Any missing data on study endpoints will be described. Adjustments for missing endpoint data will be performed only if deemed necessary and will be described completely. In the case of evidence showing systematic patterns of missing data (“informative” missing data), alternative strategies for analyzing the data, depending on the pattern of the missing, will be investigated. Secondary sensitivity analyses will be considered if necessary, and may include an analysis using multiple imputations for missing observations and an analysis in which all missing observations are considered failures.

Statistical analyses will be performed using SAS/STAT software, Version 9.2 or higher of the SAS System for Windows.

Patient confidentiality will be protected at all times, and patient identifiers will not be included in study summaries.

6.2 Sample Size Justification

This study is a single-arm, multicenter, prospective early feasibility study that is exploratory in nature. A maximum of 40 subjects will be included in the US, a maximum of 30 subjects in the Netherlands, a maximum of 30 subjects in Germany, and a maximum of 30 subjects in New Zealand

6.3 Analysis Populations

6.3.1 Screening Population

Subjects who sign the consent form but are not deemed as eligible are considered screen failures. Should a subject be a screen failure, the reason for failure will be documented, and the subject will be exited from the study.

Eligible, consenting subjects will be considered to be "Enrolled" in the study upon entering the procedure room. *Intent-to-Treat (ITT)* subjects are those who enter the study procedure room, regardless of whether they receive the study device or not. See section 6.3.2. *Implanted* subjects are those who receive the study device. See section 6.3.3.

Serious adverse events will be reported for all enrolled (Intent-to-Treat and Implanted) subjects from enrollment through the time of study exit.

6.3.2 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) population will consist of all subjects who have signed the ICF and entered the interventional suite, regardless of whether the study THV implantation was attempted or not attempted for whatever reason. [redacted] Safety reporting will include a report on this population.

6.3.3 Implanted Population

The Implanted population will consist of any subjects that receive treatment with the JenaValve Pericardial TAVR System, where treatment is defined as successful THV implantation. The implanted population represents the Primary Analysis population for this study.

6.4 Final Analyses

All final study analyses will be performed when all implanted subjects have completed the 5 year follow-up visit.

6.5 Reports for Safety

The Independent Clinical Events Committee/Data Monitoring Committee (CEC/DMC) will conduct interim safety reviews per the Charter. Information will be provided to the CEC/DMC for review, but no formal analyses will be completed.

7.0 SUBJECT POPULATION AND SELECTION

7.1 Subject Population

Adult subjects who have been diagnosed with aortic stenosis who are at high risk for SAVR as assessed by the local heart team will be considered for enrollment. A maximum of 40 subjects will be included in the study who will receive the JenaValve THV. Eligible, consenting subjects will be considered to be "Enrolled" in the study upon entering the procedure room. Subjects enrolled and receive treatment with the JenaValve Pericardial TAVR System, where treatment is defined as successful THV implantion is considered the implantation cohort. This implanted cohort t) represents the Primary Analysis population for this study.

Subjects that sign the ICF, but are found ineligible during the screening process will be considered screen failures and will be exited from the study at that time. Subjects in the "enrolled" population (Intent-to-Treat and Implanted) will have a subject ID number assigned in the electronic data capture (EDC) system. Those subjects that sign the ICF, enter the interventional suite, including those in whom the THV implantation is not attempted for whatever reason will be followed through the 30 day follow-up visit to assess safety, until serious adverse events experienced by subject are resolved, whereupon their participation in the study is complete. Protocol-specified tests are not required on subjects who did not receive the study device (i.e. implanted with commercial Transcatheter valve or surgical aortic valve replacement), however, baseline and operative data will need to be entered in the EDC for these subjects.

Subjects that sign the ICF, enter the interventional suite and receive treatment with the JenaValve Pericardial TAVR System, where Treatment is defined as successful attempt with JenaValve THV will be followed through to the 5-year follow-up visit, whereupon their participation in the study is complete.

7.2 Inclusion Criteria

1. Adult patients with severe degenerative native AS as assessed by either resting or stress echocardiography:
   - mean pressure gradient > 40 mmHg or peak jet velocity > 4.0 m/s;

   AND
   - aortic valve area $\leq$ 1.0 cm^2; OR
   - indexed aortic valve area $\leq$ 0.6 cm^2/m^2
2. Patient symptomatic according to NYHA functional class II or higher
3. Patient with high risk for SAVR (STS ≥ 8% or if STS < 8%, a documented heart team agreement determines that significant co-morbidities are not captured on STS), and heart team agrees that patient can undergo SAVR for "bail out"/to address unfavorable circumstances if necessary

4. Patient has suitable anatomy to accommodate the insertion and delivery of the JenaValve delivery system
5. Patient or the patient's legal representative has provided written informed consent
6. Patient or the patient's legal representative agrees to comply with all required post-procedure follow-up visits

7.3 Exclusion Criteria

1. Congenital uni- or bicuspid aortic valve morphology
2. Previous prosthetic aortic valve (bioprosthesis or mechanical) implant
3. Mitral regurgitation > moderate
4. Clinically significant coronary artery disease (CAD) requiring revascularization within 30 days prior to index procedure, or planned CAD revascularization procedure within 12 months after index procedure
5. Echocardiographic evidence of left cardiac thrombus
6. Endocarditis or other active infection
7. Hypertrophic cardiomyopathy with or without obstruction
8. Severe pulmonary hypertension (systolic PA pressure >80 mmHg) or severe RV dysfunction (RV fractional area change <35%, or TAPSE < 16 mm, or tissue Doppler S' <10)
9. Very severely reduced left ventricular ejection fraction (LVEF <20%)
10. Aortic annular diameter of less than 21 mm or more than 27 mm (assessed by Multi-detector CT (MDCT) measurement)
11. Aortic annulus angulation >60° (assessed by Multi-detector CT measurement)
12. Straight length of ascending aorta of < 55 mm
13. Significant disease of ascending aorta, including ascending aortic aneurysm (defined as maximal luminal diameter of 50 mm or greater) or atheroma (including if thick [>5 mm], protruding or ulcerated)
14. Need for urgent or emergent TAVR procedure for any reason
15. Cardiogenic shock or hemodynamic instability requiring inotropic support or ventricular assist device
16. Myocardial infarction < 30 days prior to index procedure
17. Cerebrovascular event (TIA, stroke) < 180 days prior to index procedure
18. Severe renal insufficiency (GFR < 30 ml/min), OR renal disease requiring renal replacement therapy
19. Blood dyscrasias as defined: leukopenia (WBC < 3000/mm^3), thrombocytopenia (platelets < 90,000/µl) or anemia (Men: Hgb < 8.1 g/dl; Women: Hgb < 7.4 g/dl)
20. Active peptic ulcer or upper gastrointestinal bleeding < 90 days prior to index procedure
21. Known hypersensitivity or contraindication to aspirin, heparin, ticlopidine or clopidogrel, nitinol, tantalum or allergy to contrast agents that cannot be premedicated
22. Contraindication to intraoperative transesophageal echocardiography and/ or MDCT
23. Estimated life-expectancy of < 24 months
24. Patient is enrolled in another investigational medical device or drug study, which has not completed the required primary endpoint follow-up. *(Note: Patients involved in a long-term surveillance phase of another study are eligible for enrollment in this study)*

25. Other medical, social, or psychological conditions that in the opinion of an Investigator precludes the patient from providing appropriate informed consent
26. Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up assessments).
27. Unable to comply with follow-up requirements

7.4 Subject Screening

Adult subjects who have been diagnosed with aortic stenosis and who are at high risk for SAVR will be screened for eligibility. All subjects screened for the study will be listed on the site's Screening Log. The log will capture the subject's gender, age, date of screening and the reason(s) for study exclusion.

7.5 Informed Consent Procedures

Written Informed Consent must be obtained for all subjects who are potential study candidates before any study specific tests or procedures are performed.

The general process for obtaining informed consent is as follows:

- Ensure that the principal investigator or his/her authorized designee conducts the informed consent process;
- Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation;
- Avoid any coercion or undue improper influence on, or inducement of, the subject to participate;
- Not waive or appear to waive the subject's legal rights;
- Use native non-technical language that is understandable to the subject;
- Provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation;
- Include personally dated signatures of the subject/subject's legal representative and the principal investigator/authorized designee responsible for conducting the informed consent process;
- Provide the subject with a copy of the informed consent form and any other written information; and,
- Ensure important new information is provided to new and existing subjects throughout the clinical investigation.

7.6 Subject Discontinuation/Withdrawal Criteria

Once the subject has been enrolled in the study, she/he may withdraw her/his consent to participate in the study at any time without prejudice. Participation in this clinical investigation is entirely voluntary. Likewise, there may be a reason identified by the Investigator that deems the subject no longer suitable for the study. In either case, the Investigator should contact the Sponsor to discuss the circumstances for discontinuation/withdrawal. Reasons for discontinuation or withdrawal may include, but are not limited to the following:

- Subject is uncooperative with compliance of required study tests, medical management and/or procedures for two (2) or more consecutive follow-up visits;
- Investigator determines that subject has developed a condition in which continued participation in the study is considered potentially harmful to the subject;
- Subject withdraws their consent;
- Subject is lost to follow-up;
- Subject incorrectly enrolled in the study; or
- The Sponsor terminates the study

7.6.1 Data collection and Follow-Up for Discontinued/Withdrawn Subjects

All "implanted" subjects in the study are considered eligible for follow-up and will be followed per the assessment schedule outlined in **Table 2 (Section 12.0)**. Subjects may withdraw at any time from the clinical trial without jeopardy or prejudice. If a subject terminates from the study, the reason for study termination will be recorded. If termination is a result of adverse event or death, an Adverse Event Form will also be completed. Subjects who withdraw consent after treatment will not be required to undergo follow-up after withdrawal, but will still be considered part of the study cohort.

Every attempt will be made to conduct an exit/final visit prior to a subject terminating from the study. The reason for early discontinuation will be documented in the source documents and electronic case report forms (eCRF).

7.7 Subjects Lost to Follow-Up

All reasonable efforts (at least 3 contact attempts via phone/email or 2 registered letters) will be made to obtain complete data for all subjects, before they are considered lost to follow-up. Missing observations may occur due to subjects who are lost to follow-up, or demonstrate noncompliance with the required assessments.

8.0 PRE-INDEX PROCEDURE METHODOLOGY

The following baseline data must be collected prior to the index procedure for all subjects meeting the inclusion / exclusion criteria:

- Signed Informed Consent
- Medical History
- Cardiovascular Medications
- STS Score
- Targeted Physical Exam (including vital signs)
- 12 lead ECG / rhythm strip
- Laboratory Tests (Complete blood count (CBC): WBC with differential, RBC with HCT and Hb, platelet count, coagulation panel (PT, PTT and an INR for subjects on vitamin-K antagonist), creatinine, urine or serum albumin, C-reactive protein, plasma-free Hb, serum LDH or haptoglobin and cardiac biomarkers (troponin I or T or CK/CK-MB)
- Echocardiography (TTE or TEE)

- Multidetector CT Scan Imaging
- NYHA Class
- MMSE (Mini Mental State Exam)
- Modified Rankin Scale (mRS)
- INR for subjects on vitamin-K antagonist anticoagulation therapy
- 6-minute walk test (6MWT)
- Kansas City Cardiac Questionnaire (KCCQ)

The procedures required for screening and baseline may be conducted during more than one visit, provided that procedures are conducted within 60 days prior to index procedure, unless otherwise noted. Appropriately acquired imaging studies (baseline multidetector CT scans and Echocardiograms) performed within 1 year of the index procedure may be used.

9.0 INDEX PROCEDURE- GENERAL DESCRIPTION

The TAVR procedure will be performed in a minimally invasive manner, using a transfemoral approach to deliver and deploy the THV.

Note: Refer to the Instructions for Use (IFU) for the device for complete details on device preparation and use.

The following data must be collected during the index procedure assessment period:

- Transesophageal Echo (TEE)
- Procedural details
- Adverse Event Assessment
- Anticoagulation/antiplatelet therapy administered intra-procedure

The index TAVR procedure may be performed in a standard operating room, hybrid operating room, or cardiac catheterization lab. In any of these settings emergency equipment and resources including adequate blood products, external defibrillator paddles, proper anesthesia administration, and monitoring capabilities must be available.

Note: A recommended technique is presented in the following sections. It is recognized that individual patient anatomic variation or surgical/interventional conditions may necessitate modifications to the outlined procedures. However, to the extent possible, physicians should adhere to the procedure steps. Unless a modification to the procedures outlined below is required for anatomic or surgical/interventional reasons, it will be considered a protocol deviation.

10.0 INDEX PROCEDURE THROUGH DISCHARGE

10.1 Antithrombotic Therapy

To protect subjects from bleeding or thromboembolic events, a recommended process for antithrombotic therapy based on AHA/ACC 2014 guidelines [Nishimura, et al., 2014] is provided below. Investigators may utilize their institutional procedures for anticoagulation/antiplatelet

therapy, in recognition of various agents available as well as individual patient factors such as CHA_2DS_2-VASC score.

10.1.1 During Index TAVR Procedure

- Time of Heparin administration must be recorded
- IV unfractionated heparin with a target minimum ACT ≥ 250-300 seconds
- ACT of >250 should be documented prior to guidewire placement
- The ACT should be measured at least every 30 minutes, starting 5 minutes after heparin administration. Additional heparin should be administered if the ACT is <250. The additional ACT should also be measured starting 5 minutes after every heparin administration. The most recent ACT should be measured and documented every 30 minutes.

The JenaValve Introducer System should be inserted only after the ACT is verified to be >250-300 seconds, and the delivery catheter is loaded and ready for use.

10.1.2 Post-Index TAVR Procedure

- Aspirin 75 – 100 mg daily by mouth, indefinitely
- Clopidogrel 75 mg daily by mouth, for 6 months
- If oral anticoagulation is indicated, no clopidogrel should be given

To monitor anticoagulation for patients on vitamin-K antagonists, International Normalized Ratio (INR) should be measured at each follow up visit. Additional INR testing may be performed according to institutional practice or the physician's discretion.

10.2 Patient Preparation in Procedure Room

The patient is prepped and draped so that the interventionalist/cardiac surgeon has access to the entire left lateral thorax, the sternum, and both groin areas.

Non-sterile, external defibrillator pads are placed behind the right shoulder and on the left flank, away from femoral insertion sites. Alternatively, if sterile external defibrillator pads are available, one can be placed over the sternum and one directly posterior on the back of the patient.

General anesthesia or conscious sedation is induced and the patient ventilated according to institutional practices.

10.3 Implantation Procedure

A femoral access for diagnostic intervention is performed in standard technique. Via a percutaneous vascular sheath a pigtail catheter is advanced into the left ventricle which is used for hemodynamic measurements and angiographic control. Aortography of the aortic root using different planes is performed at the beginning of the procedure to determine the aortic valve plane, the plane of alignment of the aortic cusps, and to identify the course of the coronary arteries.Transesophageal echocardiography (TEE) will also be used during the implantation procedure.

Through venous femoral access, a temporary pacemaker lead is inserted into the right ventricular cavity, to allow reliable rapid pacing during balloon valvuloplasty (BAV). Pre-BAV is performed through a separate sheath; see Instructions for Use (IFU) for detailed procedural information. Balloon valvuloplasty is performed as applicable per IFU, then the JenaValve Pericardial TAVR System prepared, delivered, and deployed per the transfemoral IFU.

Note: After implant of the JenaValve THV, the serial number associated with the THV should be recorded on the supplied Implant Card. The completed Implant Card is to be provided to the patient prior to discharge.

10.3.1 THV Prosthesis Assessment

After deployment the valve function is assessed by angiography and echocardiography.

10.4 Index Procedure Completion and Tissue Closure

Once all maneuvers are complete, catheters and sheaths are withdrawn. Catheter insertion site hemostasis and dressings should be performed according to institutional techniques.

The patient is awakened and extubated, at the discretion of the interventionalist(s) in consultation with the anesthesiologist, if general anesthesia was used. The patient is transferred to the recovery area.

10.5 Post-Index Procedure/ Prior to Leaving Hospital

The following items will be recorded post–index procedure, or anytime prior to discharge but no more than 10 days post-procedure (i.e. in case of prolonged hospitalization).

- Cardiovascular Medications
- Targeted Physical Exam (including vital signs)
- 12 lead ECG / rhythm strip
- Laboratory Tests (Complete blood count (CBC): WBC with differential, RBC with HCT and Hb, platelet count, coagulation panel (PT, PTT and an INR for subjects on vitamin-K antagonist), creatinine, urine or serum albumin, C-reactive protein, plasma-free Hb, serum LDH or haptoglobin and cardiac biomarkers (troponin I or T or CK/CK-MB)
- Echocardiography (TTE or TEE) including assessment of THV function
- NYHA Class
- Adverse Events
- Modified Rankin Scale (mRS)

11.0 FOLLOW-UP EVALUATIONS

Follow-up evaluations will be scheduled for 1 month, 6 months, 1 year, and annually thereafter for 5 years after the index procedure. Thereafter, the patient exits the study and is to be followed per institutional requirements for patients with transcatheter aortic valves.

11.1 Thirty (30) Days Post-Index Procedure Follow-Up Evaluation

A follow-up evaluation will be scheduled for 30 days post-index procedure (± 7 days). The following assessments will be performed:

- Cardiovascular Medications
- Targeted Physical Exam (including vital signs)
- 12 lead ECG / rhythm strip
- Laboratory Tests (Complete blood count (CBC): WBC with differential, RBC with HCT and Hb, platelet count, coagulation panel (PT, PTT and an INR for subjects on vitamin-K antagonist), creatinine, urine or serum albumin, C-reactive protein, plasma-free Hb, serum LDH or haptoglobin and cardiac biomarkers (troponin I or T or CK/CK-MB)
- Echocardiography (TTE or TEE) including assessment of THV function
- NYHA Class
- Adverse Events
- Modified Rankin Scale (mRS)

If the subject reports any adverse events that are potentially serious during the follow-up evaluation period, the subject should return to the investigator's facility for further evaluation of the event.

11.2 One hundred eighty (180) Days Post-Index Procedure Follow-Up Evaluation

A follow-up evaluation will be scheduled for 180 days post-index procedure (± 30 days). The following assessments will be performed:

- Cardiovascular Medications
- Targeted Physical Exam (including vital signs)
- 12 lead ECG / rhythm strip
- Laboratory Tests (Complete blood count (CBC): WBC with differential, RBC with HCT and Hb, platelet count, coagulation panel (PT, PTT and an INR for subjects on vitamin-K antagonist), creatinine, urine or serum albumin, C-reactive protein, plasma-free Hb, serum LDH or haptoglobin and cardiac biomarkers (troponin I or T or CK/CK-MB)
- Echocardiography (TTE or TEE) including assessment of THV function
- NYHA Class
- Adverse Events
- 6 minute walk test
- Modified Rankin Scale (mRS)

If the subject reports any adverse events that are potentially serious during the follow-up evaluation period, the subject should return to the investigator's facility for further evaluation of the event.

11.3 One (1) to Five (5) Year Post-Index Procedure Follow-Up Evaluation

A follow-up evaluation will be scheduled for 1 year post-index procedure (± 60 days). The following assessments will be performed:

- Cardiovascular Medications
- Targeted Physical Exam (including vital signs)
- 12 lead ECG / rhythm strip

- Laboratory Tests (Complete blood count (CBC): WBC with differential, RBC with HCT and Hb, platelet count, coagulation panel (PT, PTT and an INR for subjects on vitamin-K antagonist), creatinine, urine or serum albumin, C-reactive protein, plasma-free Hb, serum LDH or haptoglobin and cardiac biomarkers (troponin I or T or CK/CK-MB)
- Echocardiography (TTE or TEE) including assessment of THV function
- NYHA Class
- Adverse Events
- 6 minute walk test
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Modified Rankin Scale (mRS)

If the subject reports any adverse events that are potentially serious during the follow-up evaluation period, the subject should return to the investigator's facility for further evaluation of the event.

11.4 Study Exit

If the patient exits the study prior to completing the required assessments, the Study Exit CRF must be completed.

12.0 SCHEDULE OF ASSESSMENTS & SUBJECT EVALUATIONS

Evaluation of subjects enrolled in this study will include all tests and procedures listed in the Schedule of Assessments as outlined in **Table 2** below.

Table 2: Schedule of Assessments

Pre-procedural echocardiography (TEE or TTE) and a baseline multi-detector CT scan with Core Lab assessment are used to determine anatomical eligibility for enrollment. Following ethics committee/IRB approval and patient written informed consent, the patient will be screened for eligibility by heart teams. Final eligibility determination is made by an Independent Screening Committee evaluation of site screening records and Core Lab measurements/assessments. After the procedure, enrolled patients are to be followed immediately post- procedure, at hospital discharge, and then at 1 month, 6 months, 1 year; and annually thereafter for 5 years listed in Schedule of Assessments Table below:

Schedule of Assessments:	**Screening/ Baseline**	**Procedure (Day 0)**	**Pre-Discharge**	**1 Month**	**6 Months**	**1- to 5-years annually**
Medical History including consent	x					
STS Score	x					
Targeted Physical Exam[†]	x		x	x	x	x
Laboratory Tests[‡]	x		x	x	x	x
Pregnancy Test[α]	x					

Multi-detector CT Imaging [¥]	x					
12 lead ECG / Rhythm Strip	x		x	x	x	x
Echocardiography (TTE or TEE) [¥]	x	x	x	x	x	x
NYHA Classification	x		x	x	x	x
6 minute walk test (6MWT)	x				x	x
KCCQ	x					x
Modified Rankin Scale & Mini Mental State Exam (MMSE) [§]	x		x	x	x	x
Cardiovascular Medications	x	x	x	x	x	x
Adverse Events		x	x	x	x	x

[†] Physical exam includes overall health and physical assessment and vital signs.

[‡] Labs include a complete blood count (CBC): WBC with differential, RBC with HCT and Hb, platelet count, coagulation panel (PT, PTT and an INR for subjects on vitamin-K antagonist), creatinine, urine or serum albumin, C-reactive protein, plasma-free Hb, serum LDH or haptoglobin and cardiac biomarkers (troponin I or T or CK/CK-MB) will be assessed at baseline, discharge, 1 month, 6 months, 1 year and annually thereafter for 5 years.

[α] Only for females of child bearing potential and performed within 72 hours prior to index procedure.

[¥] Imaging procedures performed within 1 year prior to index procedure may be used for baseline, unless otherwise indicated.

[§] Modified Rankin Scale is performed for each patient at baseline and at each follow-up interval thereafter until study completion. The MMSE is performed at Screening/Baseline only unless the subject experiences a stroke

Follow-up windows: ±7 days (1-month visit); ±30 days (6-month visit); ±2 months (1- to 5-Year visits)

Note: Screening tests with the exception of imaging procedures should be performed within 60 days of index procedure.

All testing should be conducted at the investigational site. Follow-up testing may be performed at another site only if it is not possible for the patient (or the patient refuses) to return to the investigational site. In such cases, the Investigator may arrange for the study-required testing to be completed by the patient's local physician. However, it remains the responsibility of the study Investigator to ensure collection of appropriate information. Copies of source documents from the local physician must be obtained and kept in the patient's study file.

13.0 ADVERSE EVENTS

TAVR procedures to treat aortic stenosis are well described in the literature. Risks to the subjects will be clearly explained in the Clinical Risk/Benefit Analysis Section (see **Appendix 1 - Clinical Risk/Benefit Analysis**).

13.1 General Adverse Event Definitions

Adverse event: is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other

persons, whether or not related to the investigational medical device (see **Appendix 2 – Adverse Event Definitions**).

Adverse Event Identification: a condition that is one of the following:

a) A unique symptom or event that is a change from the patient's baseline status
b) A series of symptoms or events that can be categorized as a single entity based on definitions found herein
c) A specific diagnosis responsible for a clinical change
d) A worsening or exacerbation of a pre-existing condition

Serious Adverse Event: A serious adverse event (SAE) is any untoward medical occurrence that**:**

- Results in death
- Led to serious deterioration in the health of the subject, that either resulted in:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

Serious Adverse Device Effect (SADE)

An adverse device effect that has resulted in any of the consequences characteristics of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)[1]

A serious adverse device effect which by its nature, incidence, severity or outcome, has not been identified in the current version of the risk analysis report.

13.2 Adverse Event Classification

Adverse events will be assigned an attribution according to the Investigator's believed primary cause. Events will be categorized by relationship to the investigational device, index procedure, concomitant medications, pre-existing condition, intercurrent condition, intercurrent intervention, or other.

Investigational Device Related Adverse Event: An adverse event, which in the judgment of the Investigator, results from use of the JenaValve Pericardial TAVR System.

Procedure Related Adverse Event: An adverse event which, in the judgment of the Investigator, results as a consequence of the index procedure.

Concomitant Medication-Related Adverse Event: an adverse event is considered to be concomitant medication related when, in the judgment of the Investigator, it is reasonable to believe that the

[1] Equivalent to unanticipated adverse device effect (UADE). Refer to Section 13.4.2 of this document for further details.

event is associated with concomitant medications used in conjunction with the investigational device and is not otherwise specific to the investigational device (e.g. bleeding associated with anticoagulation medication).

Pre-Existing Condition-Related Adverse Event: an adverse event is considered to be related to a pre-existing condition when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with the patient's pre-existing condition and is not specific to the investigational device or index procedure. Pre-existing conditions that are aggravated or become more severe during or after the index procedure should be evaluated on a case-by-case basis to determine if the event may be more appropriately classified as device or index procedure-related.

Intercurrent Condition: It is reasonable to believe that the event is directly associated with an intercurrent condition/co-morbidity.

Intercurrent Intervention: It is reasonable to believe that the event is directly associated with an intercurrent intervention which was performed for reasons other than to address a device- or index procedure-related complication.
Unknown: The adverse reaction cannot be judged because information is insufficient or contradictory, and cannot be supplemented or verified.

The Sponsor, or its designee, in cooperation with the Investigator, will assess all serious adverse events considered device-related for potential reportability to the FDA as an Unanticipated Adverse Device Effect (UADE).

The Investigator should follow all unresolved serious adverse events until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, or the adverse event is otherwise explained.

13.3 Events Expected to Occur with Index-Procedure

For purposes of this study, the following events are not considered reportable adverse events because they are normally expected to occur in conjunction with treatment of Aortic Stenosis or structural heart interventional procedures, or are associated with customary, standard care of subjects undergoing minimally invasive cardiovascular intervention:

- Chest pain without associated enzyme/ECG changes
- Post-operative pain
- Post-anesthesia emesis, nausea, or headache (within 48 hours of procedure)
- Electrolyte imbalance without clinical sequelae following procedure, even if requiring correction
- Pre - Planned future Surgical Procedures
- Low grade temperature increase ($\leq$101°F or $\leq$38.5°C)
- Dizziness: Imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, lightheadedness, unsteadiness or vertigo
- Elevated White Blood Count, outside the standard laboratory normal value, without signs and symptoms of infection
- Post-operative hematocrit decrease from baseline, not associated with hemodynamic changes, remaining above 25% and requiring < 2 units PRBC's

- Minor, localized tenderness, swelling, induration, oozing, etc. at surgical site
- Sinus bradycardia/tachycardia that does not require treatment or intervention
- Trace/trivial or mild paravalvular or transvalvular leak not requiring intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention
- Any blood transfusions during preplanned operative procedure and unrelated to an adverse event
- Thrombocytopenia: does not become an AE until treatment is administered
- Atelectasis: collapse of lung tissue affecting part or all of one lung; the alveoli are deflated (not considered to be an AE unless treatment other than Chest PT is required or it prolongs hospitalization)
- Hyperglycemia: The use of insulin in the post op period does not constitute hyperglycemia if during the same hospitalization. An elevated blood sugar of less than 250 mg/dl during the first 48 hours post op does not constitute hyperglycemia
- Pleural effusion unless treatment with thoracentesis or chest tube insertion is required
- Pericardial effusion without hemodynamic compromise or treatment
- Atrial Fibrillation / Atrial Flutter / Atrial Tachycardia with or without cardioversion

This listing of events is intended to provide guidance to the investigational sites for the purpose of adverse event reporting. The Investigator at the investigational site should utilize his/her own clinical judgment in evaluating adverse experiences, and may decide that the above events should be reported as adverse events.

13.4 Adverse Event Reporting Requirements

13.4.1 General Reporting Requirements (Non-Serious Adverse Events)

All adverse events must be recorded on the Adverse Event Electronic Case Report Form (eCRF) by the Investigator (or designee). The report should include: severity, duration, action taken, treatment outcome and relationship of the adverse experience to the study device, procedure, concomitant medications, pre-existing condition, etc. (i.e., unrelated, related or relationship unknown).

The Investigator must also adhere to the following criteria:

- Use separate Adverse Event Form(s) to document each series of events
- The Adverse Event Form(s) causality must be assessed by the Investigator or co-Investigator/sub-investigator
- It is the responsibility of the Investigator to inform their IRB/EC of serious adverse events as required by their IRB/EC procedures and in conformance with FDA requirements

13.4.2 Reporting Requirements (Serious & Unanticipated Adverse Events)

All serious and any unanticipated adverse device effects must be reported by the Investigator (or designee) by submitting the Adverse Event Electronic Case Report Form or via email to the sponsor, within 24 hours of learning of the adverse event.

The Investigator (or designee) shall send a written report including a narrative description of the serious and/or unanticipated adverse event to the Sponsor or its designee within three (3) working days of the initial report.

The Sponsor will evaluate all serious adverse events for reportability as an unanticipated adverse device effect in accordance with 21 CFR part 812.46(b)[2]. The investigator and sponsor will comply with reporting requirements per 21 CFR part 812.150. A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

Any unanticipated adverse events: (including all deaths and/or serious adverse device effects) must also be reported to the FDA, all reviewing IRB's/EC's and participating investigators within ten (10) days of receiving notice of the serious adverse event or death, (or per local IRB/EC requirements), and documentation of the report sent to the Sponsor or its designee.

13.5 Patient Death

Patient death during the investigation must be reported via telephone or with written documentation to the Sponsor or designee within 24 hours of Investigator's knowledge of the death. Notification can be made by entering the CRF in the database or providing an email notification to a representative of the Study Team (i.e. site monitor, study manager) and include a brief description of the relevant details of the death. The electronic Adverse Event Form must be electronically signed by the Investigator once finalized. A copy of the death records, death certificate and an autopsy report (if performed) are required to be sent to the Sponsor or designee following the death. In addition, patient death must be reported to the IRB/EC in accordance with IRB/EC requirements.

13.6 Treatment Failures & Device Malfunctions

All reported device observations, malfunctions or failures for the JenaValve Pericardial TAVR System are required to be documented on the Procedure / Device Observation Case Report Form. In the event of a suspected observation or device problem, the device shall be returned to the Sponsor for analysis. Instructions for returning the investigational device are included in the Study Reference Manual.

14.0 STUDY OVERSIGHT

14.1 Independent Subject Screening Committee

An Independent Subject Screening Committee (ISSC) will be established under the direction of the Sponsor. The role of the ISSC is to review key information on subjects and establish their final eligibility for participation in the study. ISSC review shall occur after the investigational site heart team has established initial eligibility of a subject. Screening Committee members shall not participate in ISSC review of their own site's patients.

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[2] Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

14.2 Clinical Events Committee/Data Monitoring Committee (CEC/DMC)

A Clinical Events Committee/Data Monitoring Committee (CEC/DMC) will be assembled prior to patient enrollment and will be comprised of leading physician practitioners and a biostatistician who are not investigators in the trial and who are not affiliated with the investigation sites. Membership of the committee shall remain anonymous to the investigational sites to reduce any potential bias.

[redacted]

14.3 Core Laboratory

An independent CT scan imaging core laboratory will be utilized for assessment of baseline multidetector CT scans. All CT scan image acquisition shall be performed in accordance to the core laboratory's recommended protocol which is provided to the sites in the Study Reference Manual.

An independent echocardiographic imaging core laboratory will be utilized for assessment of echocardiograms. All echocardiogram image acquisition shall be performed in accordance to the core laboratory's recommended protocol which is provided to the sites in the Study Reference Manual.

15.0 ADMINISTRATIVE RESPONSIBILITIES

The JenaValve AS EFS study will be performed in accordance with Good Clinical Practice Guidelines, the Code of Federal Regulations Title 21 CFR Parts 812, 50, 54, 56, 45 CFR Part 46, the MDD 93/42/EC, and ISO 14155, as applicable.

15.1 Institutional Review Board (IRB)/ Ethics Committee (EC) Approval

The Clinical Investigational Plan shall be reviewed and approved by the US FDA and the Investigator's Institutional Review Board/ Ethics Committee prior to patient enrollment. All proposed changes to the investigational plan must be reviewed by the Sponsor, and /or their

authorized agent, prior to implementation. Significant changes to the investigational plan must be approved in writing by the Sponsor, the IRB/EC and FDA, prior to implementation. A significant change is one which may increase the risk or present a new risk to a patient, or which may adversely affect the scientific validity of the study.

Prior to shipment of the investigational study devices, a signed copy of the IRB/EC approval letter identifying the clinical study and investigational site is required to be submitted to the sponsor signifying study approval. Investigators are responsible for obtaining and maintaining annual renewal of the study by their IRB/EC (or according to renewal schedule imposed by the IRB/EC). Evidence of renewal and continued IRB/EC approval must be provided to the Sponsor or its designee accordingly.

15.2 Informed Consent

If the patient meets all clinical eligibility criteria, the patient (and/or their authorized legal representative) should be approached to obtain written informed consent. The background of the proposed study and the benefits and risks of the procedures and study should be explained to the patient or the patient's legally authorized representative. The patient or patient's legally authorized representative must sign the consent form prior to enrollment. Failure to obtain signed informed consent renders the patient ineligible for the study. All enrolled subjects will complete the appropriate consent form that has been approved by the FDA, the institutional review board (IRB)/ ethics committee (EC) and the Sponsor (see sample in the Study Reference Manual). Copies of the signed informed consent shall be kept in the patient's medical records and study files. A copy of the informed consent form must be given to each patient (or their authorized legal representative) enrolled in the study.

Modifications to the Study Informed Consent must have approval from the Sponsor, the IRB/EC, and FDA as required.

15.3 Confidentiality

All information and data sent to the Sponsor or their authorized designees, concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the patient.

The investigator must assure that the subject's anonymity will be maintained and that the confidentiality of records and documents that could identify subjects will be protected, respecting the privacy of and confidentiality rules in accordance with applicable regulatory requirements, including all applicable provisions of the Health Insurance Portability and Accountability Act (HIPAA) and its current regulations.

- Subjects must be identified only by their assigned study number and initials on all CRFs and other records and documents submitted to the Sponsor, the monitor, and other authorised parties
- The investigator will keep a Patient Identification List with complete identification information (name, address, contact number, informed consent version number) on each subject

- Documents not for submission to the Sponsor such as subject written informed consent forms should be maintained by the investigator in strict confidence

The subject should also be informed about the use of his/ her health information collected during the study (study data).

15.4 Data Monitoring and Quality Control

Data Monitoring

All required data for this study will be collected on standardized Case Report Forms (CRFs). The Investigator (or designated hospital staff) will assure primary data collection based on source-documented hospital chart reviews. Independent monitoring will be performed to ensure that the investigator and his/her study team conduct the clinical investigation in accordance with contract specifications, protocol, Declaration of Helsinki, Good Clinical Practice according to ICH E6 and applicable regulations, to ensure adequate protection of the rights and safety of subjects and the quality and integrity of the resulting data.

If a clinical monitor becomes aware that an Investigator is not complying with the requirements mentioned above, the Sponsor will be notified by the monitor. The Sponsor will evaluate the non-compliance and if necessary, immediately either secure compliance or discontinue shipments of the investigational device to the Investigator and terminate the Investigator's participation in continued enrollment in the investigation. The Investigator will be required to return all unused devices to the Sponsor.

Source Documentation

Auditors, monitors, Institutional Review Boards (IRBs), the Sponsor, and regulatory authorities may have access to the medical records related to this study. Original or certified copies of all relevant clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the medical file of each enrolled Subject. At a minimum, the following must be included in each Subject's file:

- Sufficient medical history and current physical condition, including any medication(s) the Subject is taking at the time of the procedure to assess the Subject's eligibility;
- The medical file should reveal the Subject's participation in this study, including documentation of written informed consent;
- Dated report of the investigational procedure including medication, material usage, and complications, if applicable;
- Dated reports of the discharge and follow-up assessments;
- Dated results of required laboratory tests;
- Any adverse event(s), the resultant action or treatment, and outcome, if applicable; and

In the case of withdrawal of subject consent, reason and subject status at time of withdrawal.

The Investigator will permit study-related monitoring, audits, IRB review and authority inspections by allowing direct access to the source data. In case of electronic source data, access will be granted to the Sponsor. JenaValve Technology, Inc. in collowill monitor and manage the data for the investigational study.

15.4.1 Training

The training of clinical site personnel will be the responsibility of the Sponsor. Sponsor is responsible for housing the database and providing training on the Electronic Data Capture (EDC) System and data entry functions. . This procedure may only be performed by qualified investigators, familiar with TAVR procedures and techniques. A formal training program consisting of didactic and interactive sessions will be performed with participating investigators and study personnel identified at each site prior to patient treatment. The Sponsor or affiliated personnel shall be available to assist with the technical aspects of the device/procedure. The JenaValve Clinical Study Team or designee shall be available for protocol related training. Training will be documented. It is ultimately the responsibility of the Investigator to ensure all clinical site personnel participating in this trial are trained.

To ensure uniform data collection and protocol compliance, appointed monitors will perform study initiation visits to review the clinical protocol, techniques for the identification of eligible subjects, instructions on in-hospital data collection, methods for soliciting data from alternative sources, and schedules for follow-up with study site personnel. This initiation/ training is aimed to take place at the same time as device training.

15.4.2 Electronic Case Report Forms

Electronic Case Report Forms (eCRFs) will be used to collect all patient data during the course of the study. The eCRFs must be fully completed for each subject and electronically signed by the Investigator when complete.

Federal Regulations and Good Clinical Practice Guidelines require that Investigators maintain information in the study patient's medical records that corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, the following information should be maintained:

- Medical history/physical condition of the study patient before involvement in the study sufficient to verify protocol entry criteria
- Dated and signed notes on the day of entry into the study including the study investigator, study name, patient number assigned and a statement that consent was obtained
- Dated and signed notes from each study patient visit with reference to the CRFs for further information, if appropriate (for specific results of procedures and exams)
- Information related to adverse events.
- Study patient's condition upon completion of or withdrawal from the study
- Discharge summaries/procedure reports

15.4.3 Data Reporting

The Investigator or designated individual shall be responsible for recording all study data on the electronic case report forms (eCRFs) supplied by the Sponsor or its authorized representatives.

The Investigator is required to electronically sign the eCRFs to verify that he/she has reviewed and agrees with the recorded data. All protocol deviations shall be documented and a justification for any missed assessments shall be provided on the Protocol Deviation Case Report Form.

Completed eCRFs will be verified by the monitor at the investigational sites at regular intervals throughout the study. The Investigator will allow the monitor and/or representative of the Sponsor, and any regulatory body to review and inspect the study files, patient eCRFs, patient medical records and other related study documents as required.

15.4.4 Data Review

CRFs will be reviewed for completeness and clarity. Missing or unclear data will be investigated by the monitor and will be retrieved, clarified and entered by study personnel as necessary throughout the study. The Sponsor or their authorized representatives, may request additional documentation from the investigator such as physician procedure notes or physician written summaries when adverse events are observed and reported. Adverse events reported during the study shall be adjudicated by the Clinical Events Committee/Data Monitoring Committee (CEC/DMC) per the Charter.

Development of the primary database for the study will be performed by the Sponsor or designee. The Sponsor or designee will also be responsible for the quality control of the database and confirming the overall integrity of the data.

15.5 Record Maintenance

15.5.1 Records

The following records must be maintained in designated JenaValve AS EFS study administrative files:

- Clinical protocol and all amendments
- Signed Investigator Agreement
- Institutional Review Board/Ethics Committee Approval Letter(s) including IRB/EC-approved informed consent(s) (including any revisions)
- CV for all investigators
- Correspondence relating to this study
- Correspondence with the IRB/EC
- IRB/EC membership list and/or assurance number
- Investigational site authorized study personnel signature list
- Device Instructions for Use
- Lab certification, including a set of the lab's normal range for tests performed
- Printed copy of blank set of CRFs and instructions for completion
- Patent Screening & Enrollment Log
- Site Visit Log (e.g. for Monitor sign-in)
- Investigational Device Accountability Log with invoices, including: date, quantity, lot numbers of all devices, device returns and identification of all persons the device was used on
- Adverse Event Log

- Reports (includes Adverse Event reports and final reports from Investigator and Sponsor)

The following records must be maintained for each patient enrolled in the study:

- Signed patient consent forms
- Copy of final completed CRFs
- All lab and testing results
- Record of any complications, adverse events, device problems and/or malfunctions, with supporting documentation
- Procedure reports, progress notes, physician and/or nursing notes, and patient office files
- Records pertaining to patient deaths throughout the course of the study (including death records, death certificate and autopsy report, if performed)

15.5.2 Investigator Reports

Investigators are required to prepare and submit the following complete, accurate and timely reports on this clinical investigation when necessary. Investigator files containing all records and reports of the investigation should be retained by the sites for a minimum of two (2) years after the completion/ termination of the investigational study. They may be discarded upon written notification by the Sponsor. To avoid error, the Principal Investigator should contact the Sponsor, before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

In addition, in accordance with the Clinical Study Agreement, the Sponsor should be contacted if the Principal Investigator plans to leave the investigational site so that appropriate arrangements for file custodianship can be made.

15.6 Investigator's and Sponsor's Annual and Final Reports

Each year, at a minimum, an annual summary report shall be prepared by the Investigator to provide a summary of the number of subjects treated to date as well as other pertinent clinical information associated with the investigational procedure. The annual report is required to be provided to the IRB/EC and the Sponsor or their authorized agent.

The Sponsor or its designee will be responsible for preparing a compilation of all of the participating site results for submittal as an annual progress report to the US FDA.

Upon completion and/or termination of the study a final report shall be prepared. This report will contain a critical evaluation of all data collected during the course of the investigation at each institution. The Sponsor or its designee is responsible for preparing this compilation to Investigators for submittal as a final report to their reviewing IRB/EC. The Sponsor or its designee will also provide this final report to the US FDA.

15.7 Investigational Site Monitoring

The Sponsor is responsible for monitoring the safety and effectiveness of this study. The Sponsor may utilize the services of a CRO or independent contractors to facilitate the monitoring process. The study will be monitored according to applicable provisions of JenaValve Technology, Inc. or designees clinical monitoring procedures and in compliance with Title 21 CFR Part 812.

15.8 Deviations from Clinical Protocol and Medical Emergencies

The investigator will not deviate from the clinical protocol without the prior written approval of the Sponsor except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the patient's risk or affect the validity of the study. In medical emergencies, prior written approval for protocol deviations will not be required, but the Sponsor or its designee must be notified via telephone or email within 24 hours of occurrence.

15.9 Investigational Site Termination

The Sponsor reserves the right to terminate an investigational site from the study for any of the following reasons including, but not limited to:

- Failure to obtain Informed Consent
- Failure to report Serious Adverse Events within 24 hours of knowledge
- Repeated protocol violations
- Repeated failure to complete Case Report Forms
- Failure to enroll an adequate number of subjects

15.9.1 Monitoring Methods

Sponsor will assign a monitor to clinical sites. The monitor will be responsible to monitor the study progress and to provide assistance throughout the duration of the study. The monitor will be responsible to train all new study staff, perform device accountability, monitor the study files to make sure all the regulatory approvals are in place, and source verify the clinical data. The monitor will also provide the study staff with any needed documentation for the study and answer questions as needed. The monitor will visit the sites according to the subject enrollment and as needed to make sure the study is being followed according to the study protocol.

15.9.2 Monitoring Plan

Prior to subject enrollment, an initiation visit will be completed at the study center to ensure the following:

- All approvals have been obtained and filed in the study regulatory binder
- The site has the infrastructure to perform the study according to the protocol
- Delegation of authority is complete

Routine monitoring will be performed according to the number of subjects enrolled in the study and/or as needed based on the study requirements.

Upon termination or conclusion of the study, the study monitor will perform a close-out visit.

15.10 Medicare Coverage Related to Investigational Device Exemption (IDE) Studies

Consistent with CMS coverage of IDE studies effective January 1, 2015 the following information is provided as part of this clinical protocol.

15.10.1 Release of Results

This clinical study will utilize a Publications Committee which will oversee the analysis of the study and author a publications policy strategy consistent with JenaValve policies and procedures. In particular, this committee will ensure that the pre-specified primary endpoint results and outcomes and information important to the scientific community are disseminated in a timely fashion (i.e., within 24 months of the end of the study) at scientific meetings and within the scientific literature. Full details of the presentation and publication strategy will be outlined in the Steering Committee Charter that will be issued before study enrollment is completed.

15.11 Protocol Amendments

Protocol amendments will be approved by the Sponsor, the Principal Investigators, the Institutional Review Boards and any necessary regulatory body before it can be implemented.

15.12 Quality Assurance and Auditing

As a quality assurance measure, the site may be audited during the course of the ongoing clinical trial as well as following completion of the trial. The audit will be conducted by sponsor personnel (or designee). The purpose of an audit is to provide an independent evaluation separate from routine monitoring or quality control functions of trial conduct, protocol and GCP compliance.

APPENDIX 1: ADVERSE EVENT DEFINITIONS

Definitions in table below are adapted from VARC-2; European Heart Journal (2012) and Journal of Thoracic and Cardiovascular Surgery (2013).

Term	Definition
Acute Kidney Injury	• **Stage 1** Increase in serum creatinine to 150–199% (1.5–1.99 × increase compared with baseline) OR increase of ≥ 0.3 mg/dl (≥ 26.4 mmol/l) OR urine output < 0.5 ml/kg/h for > 6 but < 12 h • **Stage 2** Increase in serum creatinine to 200–299% (2.0–2.99 × increase compared with baseline) OR urine output < 0.5 ml/kg/h for > 12 but < 24 h • **Stage 3** Increase in serum creatinine to ≥ 300% (> 3 × increase compared with baseline) OR serum creatinine of ≥ 4.0 mg/dl (≥ 354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l) OR urine output < 0.3 ml/kg/h for ≥ 24 h OR anuria for ≥ 12 h *NOTE: Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.*
Bleeding	**Life-threatening or Disabling Bleeding** • Fatal bleeding OR • Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR • Overt source of bleeding with drop in hemoglobin of ≥ 5 g/dl or whole blood or packed red blood cells (RBC) transfusion ≥ 4 units* **Major Bleeding** • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of 2–3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND • Does not meet criteria of life-threatening or disabling bleeding **Minor Bleeding** Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening, disabling or major * Given that one unit of packed RBC typically will raise blood hemoglobin concentration by 1 g/dl, an estimated decrease in hemoglobin will be calculated.
Death/Mortality	• **All-Cause Mortality**

Term	Definition

	• **Cardiovascular Mortality**: any of the following criteria:
	  • Death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure)
	  • Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease
	  • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
	  • All valve-related deaths including structural or non-structural valve dysfunction or other valve-related adverse events
	  • Sudden or unwitnessed death
	  • Death of unknown cause
	• **Non-cardiovascular Mortality:** Any death in which the primary cause of death is clearly related to another condition (e.g., trauma, cancer, suicide)

Myocardial Infarction	**Peri-Procedural MI (≤ 72 h after the index procedure)**
	• New ischemic symptoms (e.g., chest pain or shortness of breath), or new ischemic signs (e.g., ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q-waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality)
	AND
	• Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15× as the upper reference limit for troponin or 5× for CK-MB. If cardiac biomarkers are increased at baseline (> 99th percentile), a further increase in at least 50% post-procedure is required AND the peak value must exceed the previously stated limit
	Spontaneous MI (> 72 h after the index procedure) Any one of the following criteria:
	• Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with the evidence of myocardial ischemia with at least one of the following:
	  • Symptoms of ischemia
	  • ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB])
	  • New pathological Q-waves in two or more contiguous leads
	  • Imaging evidence of a new loss of viable myocardium or new wall motion abnormality
	  • Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and

Term	Definition
	accompanied by presumably new ST elevation, or new LBBB, and/ or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood • Pathological findings of an acute myocardial infarction

Stroke and TIA	**Diagnostic Criteria**
	• Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax or other neurological signs or symptoms consistent with stroke
	• Stroke: duration of a focal or global neurological deficit ≥ 24 h; OR < 24 h if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death
	• TIA: duration of a focal or global neurological deficit < 24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct
	• No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist
	• Confirmation of the diagnosis by at least one of the following:
	  • Neurologist or neurosurgical specialist
	  • Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone
	Stroke Classification
	• Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue
	• Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intra-parenchymal, intraventricular, or subarachnoid hemorrhage.
	• A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic.
	Stroke Definitions
	• Disabling stroke: an mRS score of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline
	• Non-disabling stroke: an mRS score of <2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline.

Vascular Access Site and Access-Related Complications	**Major Vascular Complications** • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudoaneurysm OR

Term	Definition
	• Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure, infection) leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment OR • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR • The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment OR • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR • Surgery for access site-related nerve injury OR • Permanent access site-related nerve injury **Minor Vascular Complications** • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment OR • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) OR **Percutaneous Closure Device Failure** Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)
Conduction disturbances and arrhythmias	• Baseline conduction abnormalities, paroxysmal or permanent atrial fibrillation (or flutter), and the presence of permanent pacemaker • Implant-related new or worsened cardiac conduction disturbance

Term	Definition
	(new or worsened first-degree atrioventricular (AV) block, second-degree AV block (Mobitz I or Mobitz II), third-degree AV block, incomplete right bundle branch block, right bundle branch block, intraventricular conduction delay, left bundle branch block, left anterior fascicular block, or left posterior fascicular block, including AV block requiring a permanent pacemaker implant • Persistent or transient high-degree AV block. High-grade AV block is persistent if present every time the underlying rhythm is checked • New permanent pacemaker implantation, with precise documentation of the clinical indication and the number of days from the index procedure to the pacemaker implant • New-onset atrial fibrillation (or flutter) • Any new arrhythmia resulting in hemodynamic instability or requiring therapy
Other TAVI-related complications	**Conversion to open surgery** Conversion to open sternotomy during the TAVI procedure secondary to any procedure-related complications **Unplanned use of cardiopulmonary bypass (CPB)** Unplanned use of CPB for hemodynamic support at any time during the TAVI procedure **Coronary obstruction** Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native leaflets, calcifications or dissection, occurring during or after the TAVI procedure **Ventricular septal perforation** Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVI procedure **Mitral valve apparatus damage or dysfunction** Angiographic or echocardiographic evidence of new damage (chordae papillary muscle, or to the leaflet) to the mitral valve apparatus or dysfunction (e.g. restrictions due to the THV) of the mitral valve during or after the TAVI procedure **Cardiac tamponade** Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the TAVI procedure **Endocarditis** Any one of the following: • Fulfilment of the Duke endocarditis criteria • Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation • Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy **Valve thrombosis**

Term	Definition
	Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis **Valve malpositioning** After initial correct positioning, the valve prosthesis moves upwards or downwards, within the aortic annulus from its initial position, with or without consequences **Valve embolization** The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus **Ectopic valve deployment** Permanent deployment of the valve prosthesis in a location other than the aortic root **TAV-in-TAV deployment** An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function, during or after the index procedure

REFERENCES

[1] Iung B, Baron G, Butchart E, Delahaye F, Gohlke C-Barwolf C, Levang O, Tornos P, Jet al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J.*2003;24:1231-43.

[2] Lindroos M, Kupari M, Heikkila J and Tilvis R, Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol.* 1993;21:1220-25.

[3] Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, Flachskampf F, R, Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J.* 2002;28:230-68.

[4] Frank S, Johnson A and Ross J. Natural history of valvular aortic stenosis. *Br Heart J.* 1973; 35:41-46.

[5] Schwarz F, Baumann P, Manthey J, Hoffmann M, Schuler G, Mehmel H, Schmitz W and Kubler W. The effect of aortic valve replacement on survival. *Circulation* 1982;66:1105-10.

[6] Bernard Y, Etievent J, Mourand J, Anguenot T, Schiele F, Guseibat M and Bassand J. Long-term results of percutaneous aortic valvuloplasty compared with aortic valve replacement in patients more than 75 years old. *J Am Coll Cardiol.*1992;20:796-801.

[7] Roques F, Nashef S, Michel P, Gauducheau, de Vincentiis C, Baudet E, Cortina J, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19.030 patients. *Eur J Cardiothorac Surg.*199; 15:816-22.

[8] Vaquette B, Corbineau, Laurent, Lelong B, Langanay T, de Place C, Froger-Bompas C, et al. Valve replacement in patients with critical aortic stenosis and depressed left ventricular function: predictors of operative risk, left ventricular function recovery, and long term outcome. *Heart.*2005; 91:1324-9.

[9] Piazza N, Grube E, Gerckens U, den Heijer P, Linke A, Luha O, Ramondo A, et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 F) CoreValve Revalving System: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. *EuroInterv.* 2008; 4:242-9.

[10] Bauernschmitt R, Bleiziffer S, Ruge H, Mazzitelli D, Schreiber C, Tassani-Prell P, Hutter A, et al.Kathetergestützter Aortenklappenersatz: Alternative zur offenen Chirurgie bei Hochrisikopatienten. *Z Herz- Thorax- Gefäßchir.*2009*;* 23:2-8.

[11] Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Jet al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med.* 2011;364(23): 2187-98.

[12] Leon MB, Smith CR, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010;363(17):1597-607.

[13] Holmes DR, Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement: developed in collabration with the AHA, ASE, EACTS, HFSA, MH, SCA, SCCT, SCMR. *J Thorac Cardiovasc Surg.* 2012; 144(3):e29-84.

[14] Di Mario C, Eltchaninoff H, Moat N, Goicolea J, et al. The 2011-12 pilot European Sentinel Registry of Transcatheter Aortic Valve Implantation: in-hospital results in 4,571 patients. *EuroIntervention,* 2013; 22:1362-71.

[15] Treede H, Mohr FW, Baldus S, et al. Transapical transcatheter aortic valve implantation using the JenaValve™ system: acute and 30-day results of the multicentre CE-mark study. *Eur J Cardiothorac Surg*. 41 (2012) e131–e138.

[16] Seiffert M, Bader R, Kappert U, et al. Initial German experience with transapical implantation of a second-generation transcatheter heart valve for the treatment of aortic regurgitation. *J Am Coll Cardiol Cardiovasc Interv*. 2014;7:1168-74.

[17] Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:e521–e643.

[18] Osnabrugge RL, Mylotte D, Head SJ, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol*. 2013;62(11):1002-1012.

[19] Jacobsen LA, Kent M, Lee M, and Mather M. America's Aging Population. Population Bulletin 2011. Available at: www.prb.org.

[20] Kappetein AP, Head SJ, Genereaux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur Heart J. 2012;33:2403-18.

[21] Miriam Silaschi, Hendrik Treede, et al. The JUPITER Registry: 1-year results of tansapcial aortic valve implantation using a second-generation transcatheter heart valve in patients with aortic stenosis. *Eur J Cardiothorac Surg*. 50 (2016) 874-881.