EFS amended to CE for the Harpoon Medical Device

Safety and Performance study of the Harpoon Medical Transapical Suturing Device (TSD-5) in subjects with degenerative mitral regurgitation - CE Mark Study for the Harpoon Medical Device in Poland

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Protocol Title: Safety and Performance study of the Harpoon Medical Transapical Suturing Device (TSD-5) in subjects with degenerative mitral regurgitation - CE Mark Study for the Harpoon Medical Device in Poland

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CONFIDENTIALITY STATEMENT

This study is confidential in nature. All information related to this study is considered proprietary and should not be made available to those not directly involved in this study. Authorized recipients of this information include investigators and co-investigators, other health care personnel necessary to conduct the study and Institutional Review Boards / Ethical Committees

The above personnel provided with data from this study are hereby informed of its confidential and proprietary nature. Release of this data to individuals other than those listed above requires the prior written permission of [Sponsor].

Protocol Signature pages are provided separate to this protocol		*Protocol Signature pages are provided separate to this protocol*

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I. DEFININTIONS AND ADVERSE EVENT REPORTING

Adverse Device Effect - Adverse Device Effects are adverse events that are device related. Adverse Device Effects can be classified as either Serious or Unanticipated.

Adverse Event - any untoward medical occurrence in a subject (does not imply that there is a relationship between the adverse event and the device under investigation) [equivalent to an observation]

Serious Adverse Event (SAE) - adverse event that a) led to a death, b) led to a serious deterioration in the health of the subject that

- Resulted in a life-threatening illness or injury,
- Resulted in a permanent impairment of a body structure or a body function,
- Required hospitalization or prolongation of existing hospitalization,
- Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function [equivalent to a complication]

SAEs must be reported via eCRF (electronic case report form) immediately but no later than 3 calendar days upon site awareness.

Subject - is a patient who meets the inclusion and exclusion criteria that elects to enroll in the study and provides informed consent

Unanticipated Device Adverse Event (UDAE) – 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..

UADEs must be reported to MedPass International by telephone and/or email within 24 hours upon site awareness.

II. BACKGROUND SIGNIFICANCE

Mitral Regurgitation, Transapical mitral valve repair, and the TSD-5

Mitral valve disease is the most common valvular heart disorder[i], with nearly 4 million Americans estimated to have severe mitral valve regurgitation ("MR").[ii] MR results in a volume overload on the left ventricle which in turn leads to ventricular dilation, decreased ejection performance, pulmonary hypertension, symptomatic congestive heart failure, atrial fibrillation, right ventricular dysfunction and death. Successful surgical mitral valve repair restores mitral valve competence, abolishes the volume overload on the left ventricle, improves symptom status and prevents adverse left ventricular remodeling.

The large majority of mitral regurgitation results from either **degenerative disease** (caused by elongated or ruptured native chords that fail to support the mitral valve leaflets) or **functional** ischemic or idiopathic MR (the motion of the normal mitral valve leaflets is restricted by the enlarged ventricle) both of which lead to ineffective valve closure and regurgitation.

At present 2/3rds of mitral valve procedures in North America are performed on subjects with degenerative MR and the case mix is estimated to be similar in the European Union. A common method of treating degenerative mitral valve regurgitation during open cardiac surgery involves replacing and/or supplementing elongated or ruptured chords with artificial chords made of ePTFE. While open cardiac surgery has a low mortality risk, it results in substantial disability and has important risks, including stroke, bleeding, infection, and

replacement rather than repair of the mitral valve. The ability to place ePTFE artificial cords on the mitral valve without a chest-splitting incision, cardiopulmonary bypass, or stopping the heart would represent a tremendous advance in decreasing the risk and invasiveness of mitral valve repair.

While considerable efforts have been directed toward minimally invasive chordal replacement, the only commercially available option available in the EU is a device from NeoChord Inc. The chordae replacement surgical procedure is performed using the NeoChord DS1000 device. The procedure is performed on a beating heart through a 2 to 3 inch incision between the ribs. Echocardiographic guidance is used during the procedure to aid the surgeon in positioning the device on the mitral valve leaflets. The device enters the heart through the apex, extends into the left ventricle and between the mitral valve leaflets. When the echocardiographic guidance confirms the proper position on the valve leaflets, the ePTFE suture is deployed and attached to the leaflet. The suture is then pulled through the apex of the heart as the DS1000 is removed. The correct length of the suture is determined using the echocardiographic guidance and observing the improvement in the mitral valve regurgitation in the beating heart.

Although this technology presents a minimally invasive solution for the replacement of chordae tendineae, the device requires the surgeon to enter the left ventricle with a large shaft (~10mm) for every suture. Additionally, the device limits suture placement to the free edge of the mitral leaflet and requires the operator to grasp the free edge of the moving mitral leaflet. Neochord has reported several instances of ePTFE suture tear-outs from the mitral valve leaflet. There is a need for a less invasive, beating heart cordal delivery device with more a more effective anchoring mechanism.

To address this unmet need, Harpoon Medical has developed a novel small-diameter (<3mm) rigid linear device with a needle wrapped with ePTFE in a preformed knot configuration The device may be delivered via a purpose-designed valved introducer inserted a few centimeters “off apex” just below the papillary muscle to secure cords to the mitral leaflet with a “bulky knot” anchor or directly into the left ventricle using an entry point a similar entry point. This knot is housed inside the rigid metal shaft (<3mm) of the delivery device until proper positioning is achieved on the ventricular side of the mitral leaflet with transesophageal echocardiography (TEE). To deploy and form the knot on the atrial side, a handle mechanism is actuated which advances the needle and knot through the leaflet, withdraws the needle out of the knot, then pulls the ends of the suture to form/expand the bulky knot on the atrial side of the leaflet. The ends of the suture are then released from the delivery system which can then be withdrawn from the patient leaving the bulky knot in place. The process can be repeated with additional devices to deliver additional sutures in the prolapsed leaflet. The length of the ePTFE cords sutures can be adjusted in real-time under echo guidance to optimize the surface of coaptation between leaflets before they are secured to an ePTFE pledget on the epicardium.

The Harpoon device will provide many significant advantages over current surgical interventions including: 1) a small minimally invasive incision, 2) no sternotomy, 3) no cardiopulmonary bypass, 4) no aortic manipulation, 5) a direct path to the valve plane, 6) performed on a beating heart, 7) real-time TEE-guided chordal length adjustment and 8) less complicated procedure that is teachable and adoptable. The only intracardiac implant is an

ePTFE suture which has a 25+ year history of safety in conventional mitral valve repair procedures.

Importantly, the Harpoon approach will not compromise subsequent traditional open-heart mitral valve repair or replacement procedures. Collectively, these benefits should translate into dramatically less pain and disability, lower hospital lengths of stay, fewer strokes, less renal failure, fewer wound infections and lower peri-procedural mortality.

Currently, mitral valve surgical procedures require a 3 to 6 hour procedure with 4 to 7 days of in hospital recovery (including at least a 1 day in the ICU) and a month or more of recovery before the subject can return to work. With the Harpoon device, the procedure will be transformed in to a 45 to 60 minute procedure where the subject can be discharged within 24 hours and can return to work within a week.

Treatments: At this time, there are treatments available to replace ruptured or elongated cords and result in the reduction of MR; however there is no currently effective medical therapy that treats or cures MR. The current technologies available to address the structural defects of mitral regurgitation include:

- Open heart operations to repair or replace the mitral valve. Open cardiac mitral valve operations require either a sternotomy or a thoracotomy, cardiopulmonary bypass, aortic manipulation and cardioplegic cardiac arrest. Mitral valve repair is carried out with leaflet resectional techniques (Carpentier) or nonresectional techniques using ePTFE cords placed under direct vision. Because the heart is flaccid and arrested, sizing the cords is difficult. Improper sizing of the cords may result in a failed or ineffective mitral valve repair. The success of mitral valve repair is significantly dependent on the expertise of the operating surgeon. For patients with degenerative mitral valve disease, mitral valve replacement is inferior to mitral valve repair (short-term higher perioperative mortality and long term substantially higher risks of stroke and prosthetic valve endocarditis as well as either the need for lifelong anticoagulation (mechanical valve) or the risk of repeat mitral operation (bioprosthetic valve). Mitral valve replacement (compared to repair) is a risk of open cardiac surgery. This procedure is also very invasive and not a feasible option for all patients.
- In 2008, Evalve received CE mark to market the MitraClip in the EU. Shortly thereafter, the company was acquired by Abbott Labs. The implantation of MitraClip does not involve open-heart surgery, but mimics the surgical method of edge-to-edge valve repair where the mitral valve leaflets are clipped together with the device instead of being sutured together. Extensive clinical experience with the MitraClip has been collected over the last six years and the clinical efficacy has been mixed.
- In 2013, Neochord released a CE marked, Class III medical device to the EU as a minimally invasive procedure that is performed on a beating heart to replace cords that have become elongated or ruptured. Neochord does not involve open-heart surgery, but mimics the surgical method of suturing the free-edge of the mitral valve to install replacement cords. The surgical entry point is through the apex of the heart for the deployment of a suture by the Neochord device. Initial clinical results have been promising but when the cordal suture is not properly anchored the procedure does not produce a reliable repair.

Although these procedures are available to a cardiothoracic surgeon in the EU, there is still a need for additional minimally invasive treatment options for patients suffering from mitral valve regurgitation. The MitraClip is limited to an edge-to-edge repair which is rarely used in isolation during open heart operations and has demonstrated mixed clinical efficacy. The large shaft of the NeoChord device creates significant trauma to the left ventricle and the device design limits the placement of the cordal suture to the free edge of the mitral valve leaflet which has impacted the durability of the repair. It is expected that the Harpoon Medical transapical suturing device will be a valuable treatment alternative for patients suffering from mitral valve regurgitation because it can access the left ventricle like the NeoChord device but with a smaller shaft or via a small valved introducer and has a more securing anchoring mechanism that can be deployed anywhere on the mitral valve leaflet.

III. STUDY OBJECTIVES

The purpose of this study is to evaluate the safety and performance of the Harpoon Medical TSD-5. The data collected from this trial was used to support the design of the study to support CE Mark of the TSD-5 Device. The Harpoon Medical device received CE Mark in December of 2017. Enrollment in this trial was completed as of November 2017. Follow-ups range from 12 to 36 months. The purpose of this amendment is to increase the frequency of follow-up and to extend the follow-up to 5 years post-implant.

Performance Goals:

Primary Performance Endpoints: To demonstrate that the TSD-5 performs as designed and has the ability to successfully implant one or more ePTFE cords on the mitral valve via a small left thoracotomy on the beating heart and reduce mitral regurgitation from severe to </= moderate at the conclusion of the procedure and at 30 days post-procedure.

Secondary Performance Endpoints: Severity of mitral regurgitation at 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months follow-up shall be tracked and recorded.

Safety Goals:

Primary Safety Endpoints: Procedure freedom from Serious Adverse Events (SAEs) during the ePTFE implantation procedure, at discharge, and at 30 days follow-up shall be tracked and recorded.

Secondary Safety Endpoints Freedom from Serious Adverse Events (SAEs) at 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months follow-up shall be tracked and recorded.

IV. SUBJECT SELECTION

Subjects will be screened, selected, and enrolled in this trial based on the inclusion and exclusion criteria. Once enrollment has occurred, performance of the Harpoon transapical mitral repair procedure will occur within 30 days.

Intended Use:
The TSD-5 is intended to secure ePTFE sutures on the mitral valve for the treatment of mitral valve disease.

Inclusion Criteria:

- All subjects referred for mitral valve surgery
- Presence of severe mitral regurgitation as read on an echocardiographic study performed within 60 days prior to procedure. Assessment of mitral regurgitation will be performed by the investigational site echocardiography laboratory and confirmed by the Core Echocardiography Laboratory using an integrative method.
- Age > 18 years
- Estimated post-ePTFE cordal implantation coaptation surface is adequate in the judgment of the operating surgeon and the patient eligibility committee
- Degenerative mitral valve disease
- Subject is able to sign informed consent and able to return for follow-up and is capable of participating in all testing associated with this clinical investigation
- Women of child-bearing potential have a negative pregnancy test
- Able to sign informed consent

Exclusion Criteria:

- Age < 18 years
- Infective endocarditis
- Anterior or bileaflet prolapse
- Functional mitral regurgitation
- History of Mediastinal Radiation
- Inflammatory (rheumatic) valve disease
- Requirement for concomitant cardiac surgery (e.g., coronary artery bypass grafting (CABG), aortic valve surgery, etc.)
- Symptomatic coronary artery disease
- Cardiogenic shock at the time of enrollment
- ST segment elevation myocardial infarction requiring intervention within 30 days prior to enrollment
- Evidence of cirrhosis or hepatic synthetic failure
- Pregnancy at the time of enrollment (women of child bearing age should have negative pregnancy within 14 days of surgery)
- Severe pulmonary hypertension (PA systolic pressure > 70 mmHg)
- Previous cardiac surgery, or surgery on the left pleural space
- Left ventricular, atrial or appendage thrombus
- Severely calcified mitral leaflets
- Recent stroke (< 6 months) with permanent impairment
- EuroScore (for mitral valve repair) > 8%
- Subjects with contraindications to transesophageal echocardiography
- Severe left or right ventricular dysfunction
- NYHA Class IV
- Renal insufficiency CKD stage 3b or worse (GFR < 45 ml/min/1.73 m^2)
- Patient is participating in another clinical study for which follow-up is currently ongoing. (Co-enrollment in an investigational device or interventional study)
- Patient with non-cardiac co-morbidities and life expectancy < 1 year

- Patient has a condition or conditions that, in the opinion of the Investigator, preclude participation, including willingness to comply with all follow-up procedures

V. SUBJECT ENROLLMENT

This is a prospective, nonrandomized, single-centered European study designed single arm study to demonstrate the performance and safety of the Harpoon Medical TSD-5 in Subjects with degenerative mitral regurgitation. A maximum of fifty (50) subjects will be enrolled. The estimated enrollment period is 24 months, and all subjects shall be followed for 30 days, 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, 48 months and 60 months after ePTFE implantation in accordance with the Schedule of Clinical Investigations (see below).

Subject withdrawal from the study: A withdrawal refers to a Subject who is determined to be inactive in the study due to physician discretion, Subject choice (withdrawal of consent), and loss to follow-up or Subject death. Final status will be reported on all Subjects as per the informed consent. Three documented phone calls and a registered/certified letter will be used to assure that there is minimal loss to follow-up. If these efforts to contact the Subject are unsuccessful, the Subject will be considered lost to follow-up.

Pre-procedure/baseline evaluations: All Subjects enrolled in the study will undergo transthoracic echocardiography and transesophageal echocardiography prior to surgery. These are routine preoperative studies for Subjects undergoing heart valve surgery.

Physical Assessment: All study Subjects will undergo a comprehensive history and physical examination. Once enrolled, a physical assessment must be completed within 30 days of the procedure and recorded on a Case Report Form (CRF). In addition to a physical examination and a comprehensive history, the physical assessment will include:

- Vital signs, 12-lead ECG, Laboratory assessment (including WBC count; Hemoglobin; hematocrit; platelet count; creatinine Level, Total Albumin, Total Bilirubin; INR; BNP, NTproBNP) and a chest radiograph (X-Ray)
- A serum pregnancy test for females with childbearing potential (age < 50 years) will be completed within 14 days prior to the procedure.
- As per the standard of care for valve surgery, any subject with symptoms of coronary artery disease and all subjects age >/= 45 years without risk factors shall undergo preoperative diagnostic left heart catheterization ("LHC").
- Pulmonary Function Tests, when clinically indicated
- 6 Minute Walk test

Standard transthoracic echocardiographic evaluation: Standard transthoracic echocardiographic assessment of the degree of mitral regurgitation will be performed as described in "Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography" (Zoghbi et al, J Am Soc Echocardiography 2003; 16:777-802)

An integrative approach will be used, and Subjects will be categorized as having one of:
1. None/trivial
2. Mild

3. Moderate
4. Severe

Table 1 Qualitative and quantitative parameters useful in grading mitral regurgitation severity

	Mild	Moderate	Severe
Structural parameters			
LA size	Normal*	Normal or dilated	Usually dilated**
LV size	Normal*	Normal or dilated	Usually dilated**
Mitral leaflets or support apparatus	Normal or abnormal	Normal or abnormal	Abnormal/ Flail leaflet/ Ruptured papillary muscle
Doppler parameters			
Color flow jet area‡	Small, central jet (usually < 4 cm^2 or < 20% of LA area)	Variable	Large central jet (usually > 10 cm^2 or > 40% of LA area) or variable size wall-impinging jet swirling in LA
Mitral inflow –PW	A wave dominant‖	Variable	E wave dominant‖ (E usually 1.2 m/s)
Jet density - CW	Incomplete or faint	Dense	Dense
Jet contour –CW	Parabolic	Usually parabolic	Early peaking–triangular
Pulmonary vein flow	Systolic dominance§	Systolic blunting§	Systolic flow reversal†
Quantitative parameters¶			
VC width (cm)	< 0.3	0.3-0.69	≥ 0.7
R Vol (ml/beat)	< 30	30-44 45-59	≥ 60
RF (%)	< 30	30-39 40-49	≥ 50
EROA (cm^2)	< 0.20	0.20-0.29 0.30-0.39	≥ 0.40

CW, Continuous wave; *LA*, left atrium; *EROA*, effective regurgitant orifice area; *LV*, left ventricle; *PW*, pulsed wave; *RF*, regurgitant fraction; *R Vol*, regurgitant volume; *VC*, vena contracta.

* Unless there are other reasons for LA or LV dilation. Normal 2D measurements: LV minoraxis ≤ 2.8 cm/m^2, LV end-diastolic volume ≤ 82 ml/m^2, maximal LA antero-posterior diameter ≤ 2 cm/m^2, maximal LA volume ≤ 36 ml/m^2 (2,33,35).

** Exception: acute mitral regurgitation.

‡ At a Nyquist limit of 50–60 cm/s.

† Pulmonary venous systolic flow reversal is specific but not sensitive for severe MR.

‖ Usually above 50 years of age or in conditions of impaired relaxation, in the absence of mitral stenosis or other causes of elevated LA pressure.

§ Unless other reasons for systolic blunting (eg. atrial fibrillation, elevated left atrial pressure).

¶ Quantitative parameters can help sub-classify the moderate regurgitation group into mild-to-moderate and moderate-to-severe.

VI. STUDY PROCEDURES

The surgical procedure may be completed using the valved introducer.

Entry using the valved introducer

1. General (single lumen) endotracheal anesthesia with appropriate monitoring lines (e.g. arterial line)
2. Supine position with elevation of the left hemithorax to 30 degrees
3. Performance of a small left lateral thoracotomy.
4. Placement of a purse string suture on the lateral wall of the left ventricle approximately 2 cm away from the apex.
5. Administration of systemic heparin to maintain an activated clotting time (ACT) > 350 seconds throughout the procedure, with subsequent heparin administration as needed. ACT will be checked every 20 minutes.
6. Insertion and securing of the valved introducer under echocardiographic guidance.
7. Insertion of the TSD-5 via the valved introducer.
8. Navigation to the leaflet target zone
9. Confirmation of limitation of motion of mitral valve leaflet and assurance of proper targeting.

10. Deployment of TSD-5 bulky knot suture
11. Withdrawal of the TSD-5 device through the valved introducer
12. Securing of the free ends of the bulky knot suture with a surgical snap with colored tape on the handle. Repeat Steps 7 to 12 up to four times total per valved introducer
13. Removal of valved introducer and tighten purse string suture
14. Adjust length of implanted ePTFE cords under echocardiographic guidance to minimize/abrogate mitral regurgitation and maximize leaflet coaptation.
15. Tie the properly tensioned bulky knot sutures to an ePTFE pledget, one per suture set, on the myocardium
16. Closure of thoracotomy, insertion of chest tube(s).

Conversion to Standard of Care

If in the judgment of the operating surgeon, adequate MR reduction has not been achieved, or if for any other clinical reason, conversion to standard of care (SOC) mitral valve surgery via a median sternotomy will be performed. Subjects who undergo a conversion to SOC mitral valve surgery via a median sternotomy will be followed up for 30 days.

Post-procedure management: Standard hospital protocols for the management of subjects after mitral valve surgery shall be followed. Unless other indications for anticoagulation are present, all subjects shall receive only aspirin (325 mg/day, beginning on arrival to the intensive care unit).

Discharge: All subjects will be discharged from the hospital at the discretion of the attending cardiac surgeon. Prior to dismissal all Subjects will undergo a comprehensive predismissal echocardiogram, as well as a physical assessment (vide supra) in accordance with the schedule of Clinical Investigations.

Subject follow-up: Subjects will be seen in the outpatient clinic 30 days (+10 days/-0 days) after the Harpoon procedure. A TTE and a clinical assessment shall be performed at that time (in accordance with the schedule of Clinical Investigations) to evaluate the TSD-5 device against the primary and secondary performance and safety endpoints.

Additional clinical and echocardiographic follow-up in a registry fashion shall occur for all active subjects (in accordance with the Clinical Investigations defined in the table below) at the following intervals:

- 6 months (+/- 30 days),
- 12 months (+/- 30 days)
- 18 months (+/- 30 days)
- 24 months (+/- 30 days)
- 30 months (+/- 30 days)
- 36 months (+/- 30 days)
- 48 months (+/- 30 days) and
- 60 months (+/- 30 days)

If due to an increase of MR, or due to any other medical circumstances, and a study patient has to undergo a Mitral Valve reoperation, this patient will be followed up by the study team for 30 days and then will be exited from the study.

VII. STATISTICAL ANALYSIS

The sample size for this study was determined using outcomes from available peer-reviewed literature, anticipated improvements in MR reduction at the conclusion of the procedure, at the time of the hospital dismissal and at 30 days and one year. Specifically the percentage of subjects that demonstrate MR reduction from severe to </+ moderate at the conclusion of the procedure and at 30 days. These data will be used to assess the safety and performance of the device when used on a human subject. These data will be used to assess initial safety and performance of the Harpoon Medical TSD-5, and are not designed to test a statistical hypothesis, and therefore a formal sample size has not been calculated. All data will be captured on an intent-to-treat basis. Data will be reported as descriptive statistics.

VIII. RISKS AND DISCOMFORTS

There are risks associated by our protocol. The Harpoon Medical TSD-5 device received CE Mark in December 2017. The study uses minimally invasive surgical techniques to repair/replace cords in a human heart. The discomforts we predict are equivalent to what is expected from similar operative procedures (i.e., localized pain, discomfort at the incision site(s)). Should the Harpoon Mitral Valve Repair System not perform as designed, conventional open-heart procedures will be used to facilitate the repair of the mitral valve.

IX. POTENTIAL BENFITS

The Harpoon Medical TSD-5 will provide many significant advantages over current surgical interventions including: 1) a small minimally invasive incision, 2) no sternotomy, 3) no cardiopulmonary bypass, 4) no aortic manipulation, 5) a direct path to the valve plane, 6) performed on a beating heart, 7) real-time TEE-guided chordal length adjustment and 8) less complicated procedure that is teachable and adoptable. The only intracardiac implant is an ePTFE suture which has a 25+ year history of safety in mitral valve repair procedures.

Importantly, the Harpoon approach will not compromise subsequent traditional open-heart mitral valve repair or replacement procedures

X. MONITORING AND QUALITY ASSURANCE

The clinical trial site(s) will be monitored in accordance with policies at Harpoon Medical, Inc. and those federal regulations that pertain to clinical research; namely, 21 CFR Parts 50, and 56; and others as applicable.

All SAEs (serious adverse events) and device deficiencies (reported by Investigators or identified by Safety) will be adjudicated by an independent Clinical Endpoint Committee (CEC) through the 36 month follow-up, based on relevant source documents provided from the investigational sites.

The CEC will verify SAE criteria and code. For all confirmed SAEs, CEC will also conduct a causality assessment in regards to the investigational Harpoon device and the index procedure. All adjudication activities are managed by Sponsor's Safety team according to the CEC Charter.

CLINCAL ENDPOINT COMMITTEE

A Clinical Endpoint Committee (CEC) is responsible for adjudicating all SAEs including device deficiencies which may lead to SAE through the 36 month follow-up visit. In addition, all confirmed SAEs are assessed in regards to relationship to the Harpoon device and Index procedure.

The Sponsor's Safety Department manages all CEC preparation activities according to an approved CEC Charter.

Adjudicated data is used for a final analysis. If event is not adjudicated, site reported data is used.

a. Appendix A: DATA COLLECTION SCHEDULE

General Assessment	Screening Baseline	Surgery Date	Post-Op	30 Days (30-40 days)	6 Month +/- 30 d	12 Month +/- 30 d	18 Month +/- 30 d	24 Month +/- 30 d	30 Month +/- 30 d	36 Month +/- 30 d	48 Month +/- 30 d	60 Month +/- 30 d
Informed Consent*	X											
Release of Medical Information	X											
Screening Log & Registration	X											
Medical History	X			X	X	X	X	X	X	X	X	X
Medications	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X		X	X	X	X	X	X	X	X	X	X
Laboratory Assessment	X			X								
Eligibility Criteria	X											
Screening Outcome	X											

*An additional Informed Consent Form will be signed by the subject(s) to reflect the additional follow-up required by this protocol amendment

Cardiac Assessment	Screening Baseline	Surgery Date	Post-Op	30 Days (30-40 days)	6 Month +/- 30 d	12 Month +/- 30 d	18 Month +/- 30 d	24 Month +/- 30 d	30 Month +/- 30 d	36 Month +/- 30 d	48 Month +/- 30 d	60 Month +/- 30 d
Chest X-Ray	X											
NYHA Heart Failure Class	X		X	X	X	X	X	X	X	X	X	X
6-minute walk test	X					X						
ECG	X		X	X								
TTE	X		X	X	X	X	X	X	X	X	X	X
TEE***	X	X										
Diagnostic Left Heart Cath or Clinical Standard of Care	X											
euroScORE	X											
Pulmonary Function Testing (if	X											
Quality of Life Assessment [SF-36]	X					X						

*** TEE: may be required if the TTE of the heart cannot adequately evaluate the device

RETROSPECTIVE COLLECTION OF DATA

Protocol Version 04 extends the patient follow-up to include visits at 48 and 60 months. Protocol Version 03 had introduced additional follow-up visits at 18, 30 and 36 months. These protocols allow retrospective collection of data on any scheduled or unscheduled visits for subjects who participated in the EFS or CE Mark trials (if the subject came back to the hospitals) before

Versions 03 or 04 are approved by the Ethic Committee (EC) and Competent Authority (CA). Once Protocol Version 04 has been approved by relevant EC and CA, subjects will be contacted and asked to consent to the additional visits and have their data collected. Patients who exited from the trial at 36 months as scheduled per protocol Version 03 will be contacted and requested to continue their follow-up up to 60 months as scheduled by Protocol Version 04.

Two different versions of information letters (informed consent form) will be sent depending on patient status (already exited or not). Each patient will have to sign this letter (informed consent form) to approve collection of additional data.

b. Appendix B: REFERENCES

NeoChord TACT Post-Market Surveillance Registry - To monitor the long-term performance of the CE Marked **NeoChord** Artificial Chordae Delivery System (recruiting) – Observational Study

NeoChord TACT Post-Market Surveillance Registry - Safety and Performance Study of the **NeoChord** Suturing Device in Subjects With Degenerative Mitral Valve Disease; Diagnosed With Severe Mitral Regurgitation – Ongoing but not actively recruiting
To describe the rate of subjects with at least one neochord placed using the DS1000 System AND a reduction in mitral regurgitation ≤ 2+ at the time of the procedure. Primary Outcomes: Procedure Success [Time Frame: The Subject will be evaluated from the procedure through the hospital discharge. Approximately 1 day.] [Designated as safety issue: No]

Chordal relocation for repair of anterior mitral leaflet flail: a reproducible option.
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Off-pump transapical implantation of artificial chordae to correct mitral regurgitation: Early results of a single-center experience.
Rucinskas K, Janusauskas V, Zakarkaite D, Aidietiene S, Samalavicius R, Speziali G, Aidietis A.
J Thorac Cardiovasc Surg. 2014 Jan;147(1):95-9. doi: 10.1016/j.jtcvs.2013.08.012. Epub 2013 Oct 5.

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Seeburger J, Rinaldi M, Nielsen SL, Salizione S, Lange R, Schoenburg M, Alfieri O, Borger MA, Mohr FW, Aiditeis K.
J Am Coll Cardiol. 2013 Sep 17. pii: S0735-1097(13)05160-7. doi: 10.1016/j.jacc.2013.07.090. [Epub ahead of print]

Transapical **neochord** implantation: Is tension of artificial chordae tendineae dependent on the insertion site?
Jensen H, Jensen MO, Waziri F, Honge JL, Sloth E, Fenger-Gron M, Nielsen SL.
J Thorac Cardiovasc Surg. 2013 Sep 13. pii: S0022-5223(13)00901-X. doi: 10.1016/j.jtcvs.2013.07.068. [Epub ahead of print]

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