SECURE STUDY

A POST MARKET OBSERVATIONAL STUDY TO OBTAIN ADDITIONAL INFORMATION ON THE USE OF CANGAROO ECM® ENVELOPE

STUDY SPONSOR:
AZIYO BIOLOGICS, INC.
1100 OLD ELLIS ROAD, SUITE 1200
ROSWELL, GA 30076

PROTOCOL NUMBER: 14-PR-1110
REVISION: D

FEBRUARY 7, 2018

Please Note: Confidential information contained herein is made available to you in your capacity as Investigator, Medical Advisor, or Consultant to Aziyo Biologics, Inc. It is provided only for review by you, your staff, IRB/Ethics Committee members, or other regulatory authority. Except as necessary to obtain properly informed consent for participation, it is expected that there will be no disclosure to other persons.

Investigator Statement of Compliance

I hereby agree to comply with this protocol and applicable regulations governing clinical trials, including local regulations, and Good Clinical Practice / ICH Guidelines.

Investigator Signature: _____

Date: _____

Summary of Revisions October 20, 2017	**Rationale**
Changed CorMatrix to Aziyo throughout document where applicable	Change made to correct change in ownership of company
Updated Sponsor Address	To reflect current address
Section 9: Added additional study visit	To capture AE and infection information at later time point.
Investigator Obligations	Updated to allow for trained study staff to conduct IC and other duties, as applicable.
Summary of Revision February 7, 2018	
Added information on Clindex, electronic data capture software	To provide additional information on data collection

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AZIYO BIOLOGICS, INC.

STUDY COORDINATION

STUDY SPONSOR	**AZIYO BIOLOGICS, INC.** 1100 OLD ELLIS ROAD, SUITE 1200 ROSWELL, GA 30076
DATA COORDINATION CENTER	**AZIYO BIOLOGICS, INC.** 1100 OLD ELLIS ROAD, SUITE 1200 ROSWELL, GA 30076

Study Synopsis

OBJECTIVE	The objective of the SECURE Study is to actively gather additional information on the use of the CanGaroo ECM® Envelope in a post market observational study.
STUDY POPULATION	1000 subjects who have received CanGaroo ECM® Envelope for an implantable electronic device placement.
INDICATIONS FOR USE	CanGaroo ECM® Envelope is intended to securely hold an implantable electronic device to create a stable environment when implanted in the body. The devices that may be used with the CanGaroo ECM® Envelope include pacemaker pulse generators, defibrillators, or other cardiac implantable electronic device.
ENDPOINTS	The endpoints will be defined as: 1. The proportion of subjects with CanGaroo ECM related adverse events. 2. The incidence of major pocket infection.
EXAMINATION SCHEDULE	In-office wound check, 4-6 week, 3 month and an additional visit occurring at any time point after 3 month visit following an implantable electronic device procedure utilizing CanGaroo ECM®.
CLINICAL PARAMETERS	The following clinical data will be collected at post-operative visits: • Informed Consent • Demographic information • Risk factors for infection • Implant procedure • Type of device implanted • Information on CanGaroo ECM • CanGaroo ECM related adverse events • Information on infections
ANALYSIS	Outcomes for the SECURE Study will be compared to data collected from the U.S. Healthcare Cost and Utilization Project family of databases and/or contemporary literature.

1. Introduction and Rationale

Broader indications for the implant of cardiac implantable electronic devices (CIED), a higher prevalence of systolic heart failure and population aging are the main reasons for the continuous increase in the use of pacemakers, implantable cardioverter-defibrillators and devices for cardiac resynchronization therapy. The rate of infection is out of proportion to the increase in implantation rate. This is thought to be primarily due to the associated comorbities in CIED patients, the greater complexity of the devices, and the increased duration of procedures.

The CanGaroo ECM Envelope is a 'pouch' in which a cardiac implantable electronic device is placed prior to implantation to create a stable environment and to provide a barrier between the CIED and the soft tissue of the patient and a barrier from the CIED leads.

CorMatrix Cardiovascular, Inc. received FDA 510(k) premarket clearance for the CanGaroo ECM (K140306) on August 15, 2014. This post market observational study will evaluate the safety and effectiveness of CanGaroo ECM following an implantable electronic device procedure utilizing CanGaroo ECM. Specific data will be collected at the first post-operative visit.

2. Indication for Use

The CanGaroo ECM Envelope is intended to securely hold an implantable electronic device to create a stable environment when implanted in the body. The devices that may be used with the CanGaroo ECM Envelope include pacemaker pulse generators, defibrillators, or other cardiac implantable electronic device. The entire Instructions for Use (IFU) can be found in Appendix **C.**

3. Description

The CanGaroo ECM is constructed from a multilaminate sheet (4-ply) of decellularized, non-crosslinked, lyophilized extracellular matrix (ECM) derived from porcine small intestinal submucosa (SIS). SIS is a natural collagen construct derived from a select layer of tissue that is recovered from porcine small intestine. During processing, the inner and outer muscle layers of the intestine are removed, leaving an intact, decellularized, submucosa with a portion of the tunica propria layer attached to the inner surface. The CanGaroo ECM Envelope will be provided sterile and is intended for single use in a single patient only. Over time, the device will be reinforced by cellular infiltration and tissue growth that will integrate the CanGaroo ECM Envelope.

4. Prior Clinical Evaluations

ECM has been studied in previous prospective clinical evaluation, and a post-market clinical study is ongoing. The ECM for Pericardial closure has been studied in a randomized, prospective study to evaluate its ability to reduce the incidence of new onset atrial fibrillation; the ECM for Carotid Repair is under evaluation in a post-market study to capture and assess device performance data from subjects undergoing patch angioplasty of the carotid artery following carotid endarterectomy using the product per its FDA-cleared Indications for Use; and a post market study to capture additional information (RECON) from subjects undergoing a procedure requiring pericardial closure using the product per its FDA-cleared Indications for Use.

4.1. Clinical Evaluation of the ECM Pericardial Closure Device

The ECM Pericardial Closure device was evaluated in a multicenter, prospective, randomized, controlled clinical study, to demonstrate the safety and effectiveness of the device to reduce the incidence of new onset postoperative atrial fibrillation by circumferentially reconstructing the normal pericardial anatomy following isolated, first-time, coronary artery bypass grafting (CABG) procedures as compared to the control group subjects who did not undergo pericardial closure. Safety was to be established by demonstrating that the composite clinical event rate for the ECM group was not worse than the control group. Effectiveness was to be established by demonstrating a reduced incidence of new onset post-operative atrial fibrillation in the ECM group as compared to the control group. 440 patients at 15 U.S. sites were enrolled between December 2010 and November 2012 and randomized in a 1:1 ratio into either the ECM group (pericardial closure) or the control group (no pericardial closure). A blinded, independent core laboratory evaluated all arrhythmia data to determine if subjects met the effectiveness endpoints. A blinded, independent Clinical Events Committee adjudicated all safety endpoint events. Patients were evaluated at hospital discharge, 30 days and 270 days postoperatively. Subjects were adults (at least 18 years of age) with no prior history of atrial fibrillation or history of anti-arrhythmia drug treatment in the past three months and no implantable cardiac devices (i.e., cardiac resynchronization therapy devices with and without defibrillator capabilities [CRT-Ds and CRTs), implantable cardioverter-defibrillators [ICDs] and pacemakers) undergoing isolated, first-time CABG with a median sternotomy approach.

The primary effectiveness endpoint, superiority of the ECM over no pericardial closure for reduction in the incidence of new onset post-operative atrial fibrillation, was not met. The study results showed that the rate of new onset post-operative atrial fibrillation for the primary effectiveness endpoint was similar between the two groups, with a rate of 38.3% in the ECM group compared with 35.9% in the control group. The two secondary effectiveness endpoints, the rate of treated or sustained episodes of new onset postoperative atrial fibrillation (defined as a single episode that last 15 minutes or more) and the rate of treated episodes of new onset postoperative atrial fibrillation showed results were also similar between the two groups.

The composite primary safety endpoint event rates for the ECM and control group were 3.9% and 3.7%, respectively. Using the protocol specified non-inferiority margin, 7.5%, the ECM was shown to be non-inferior to control for the primary safety endpoint ($p<0.001$). Therefore, the primary safety endpoint for the study was achieved. The composite secondary safety event rate was similar for the two groups (5.8% for the ECM group compared with 3.9% for the control group) demonstrating no significant increase in the rate of bypass graft failure in the ECM group compared with the control group.

Although the study failed to demonstrate a reduction in the incidence of new onset post-operative atrial fibrillation, the study demonstrated that the ECM for Pericardial Closure continues to be safe for its intended use, with no significant increase in the rate of bypass graft failure or cardiac tamponade compared with no pericardial closure.

4.2 Post-market Clinical Evaluation of the ECM for Carotid Repair

Aziyo is currently conducting a post-market registry study for the ECM for Carotid Repair (Protocol No. 11-PR-1021). The objective of this registry is to capture and assess device performance data from subjects undergoing patch angioplasty of the carotid artery following carotid endarterectomy using the ECM for Carotid Repair per its commercial Indications for Use. This registry provides an ongoing post-market surveillance mechanism to document clinical outcomes on the use of the ECM for Carotid Repair. This is a multi-center, prospective, single-arm, post-market, observational registry of subjects receiving the ECM for Carotid
Repair for patch angioplasty following carotid endarterectomy procedures. This post-market registry may involve up to ten U.S. clinical sites and up to 230 subjects. Data will be collected through the 24-month follow-up.

One-hundred and eighty-six patients are enrolled in the study and included in the interim analysis of the ECM for Carotid Repair registry. The data demonstrated that the rate of device related adverse events were consistent with the rates found in the review of the contemporary literature for patch angioplasty. Specifically, no unanticipated events were found and the rate of the events was as anticipated in the risk management plan. Of specific interest in the analysis was the rate of pseudoaneurysm, which was present in 2 (1.08%) of the 186 patients and compared favorably to the rates found in the literature (1.4% to 5%).

The mean carotid stenosis (maximum) at pre-operative was 84.8%. Mean change from baseline values were -56.8%, -57.9%, and -59.6% at the 1 to 3-month, 6-month, and 12-month follow-up evaluations. The mean carotid stenosis (minimum) at pre-operative was 71.7%. Mean change from baseline values were -63.9%, -61.2%, and -63.4% at the 1 to 3-month, 6-month, and 12-month follow-up evaluations.

As a result of this analysis and the directed and ongoing risk management activities, the overall residual risk of the ECM for Carotid Repair is determined to be acceptable.

5. Study Objectives

The objective of the SECURE Study is to actively gather additional information on the use of the CanGaroo ECM® Envelope in a post market observational study.

Endpoints

The endpoints will be defined as:

1. The proportion of subjects with CanGaroo ECM related adverse events.
2. The incidence of major pocket infection.

Major infection will be defined as 1) superficial cellulitis in the region of the CIED pocket with wound dehiscence, erosion or purulent drainage, 2) deep incisional or organ/space (pocket) surgical site infection, 3) persistent bacteremia or 4) endocarditis. Minor CIED infections include any that do not meet the definition of a major CIED infection. Documentation will also be provided in the medical records.

6. Study Design

This is a multi-center post-market observational study. It is anticipated that up to 1000 subjects will be enrolled at up to 50 centers. Eligible candidates will be approached to ascertain interest in study participation at their initial follow up visit. If a subject is interested in participating and has had CanGaroo ECM used in their procedure, they will be asked to allow their physician to use their medical information from the procedure and four follow up visits. An informed consent will be provided to the patient and the patient will be asked to sign unless a Waiver of Documentation of Consent has been obtained. If a Waiver of Documentation of Consent is in effect, all elements of the approved informed consent will be provided verbally and the process will be documented in the subject study binder by the research staff for either method of consent.

7. Study Population

The study population will consist of any subject who has received the CanGaroo ECM® Envelope for an implantable electronic device placement. Subjects will be considered enrolled into the study once they have provided informed consent and completed the procedure using the CanGaroo ECM Envelope. Before any subject can be enrolled, the site must have IRB approval from a centralized IRB or their specific institution IRB for the protocol and Informed Consent Form to be used at that site and Waiver of Documentation of Consent, if applicable.

8. Study Methods

Study procedures are standardized to the extent possible and all study-related data will be captured on a standardized Case Report Form and entered by sponsor personnel into Clindex, Version 3.11.0.1027R, an electronic data capture software. A copy of the Case Report Form is provided in Appendix B.

9. Study Procedures

Patients return for an in-office wound check, a 4-6 week, 3 month and any visit following the 3 month visit depending on the investigator's standard of care for follow up. If the subject is unable to return to the clinical site for all visits, the site may contact the subject or the referring physician to provide follow-up data to study site by telephone.

The following information collected and documented:

- Informed Consent
- Demographic information
- Risk factors for infection
- Implant procedure
- Type of device implanted
- Information on CanGaroo ECM
- CanGaroo ECM related adverse events
- Information on infections

All study-related data will be captured on a standardized Case Report Form. A copy of the Case Report Forms is provided in Appendix B. Case report forms will be sent to Aziyo via email or fax.

Stephanie Beall
Aziyo Biologics, Inc.
1100 Old Ellis Road, 1200
Roswell, GA 30076
(470) 514-4031 Direct Office
(678) 566-2680 Fax
sbeall@aziyo.com

10. Adverse Event Reporting

10.1 Definitions

Adverse Event (AE)

Adverse event (AE) will be defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs in subjects whether or not related to the device. This includes events related to the device and to the procedure involved. For this post market clinical study only events that relate to the use of the CanGaroo ECM will be collected and is defined below in Adverse Device Effect.

Adverse Device Effect (ADE)
An Adverse Device Effect is defined as a clinical sign, symptom, or condition that is causally related to the device procedure, the presence of the device, or the performance of the device. Due to the temporal proximity of the AE to product administration, there is a reasonable possibility that the product may have caused the AE or may have contributed to the severity or duration of an event caused by other means.

Serious Adverse Event (SAE)
A serious adverse event is defined as an event that: a) led to death, b) led to serious deterioration in health that either:

1) Resulted in life threatening illness or injury, or
2) Resulted in a permanent impairment of a body structure or body function, or
3) Required in-patient hospitalization or prolongation of existing hospitalization, or
4) Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

A planned hospitalization for pre-existing condition without a serious deterioration in health, is not considered to be a serious event.

10.2 Assessing and Recording Adverse Events

Each AE recorded must be documented on the Case Report Form. All serious and device related events must be reported immediately to Aziyo via telephone or email within 24 hours of the Investigator becoming aware of the event. The case report form will be submitted to Aziyo. The site will be contacted by Aziyo for additional information including, but not limited to:

- Description of the event and underlying cause (diagnosis), coexisting disease, or other. The AE should be recorded in standard medical terminology rather than the subject's own words when possible.
- Date of onset and date of resolution. If the event is present at the single post-operative visit it will be noted as unresolved.
- Intensity of the event: mild, moderate, or severe.
- Frequency of the event: single episode, intermittent, or continuous.
- Action taken: none, medication, procedure, medication and procedure, or other.
- Relationship to the device/procedure/surgery: not-related, possibly-related, or probably-related.

The Investigator must ensure that the details of the event are documented in the medical notes including full details of the outcome, in addition to recording the event on the case report form.

All procedure and device related serious adverse events that are associated with the use of the device will be evaluated in accordance with the protocol and the Sponsor's Incident/Event Reporting SOP. Any serious adverse event that requires a Medical

Device Report will be reported by the Sponsor to the FDA in accordance with Sponsor's Medical Device Reporting SOP. The site should contact:

Stephanie Beall
Aziyo Biologics, Inc.
1100 Old Ellis Road, 1200
Roswell, GA 30076
(470) 514-4031 Direct Office
(678) 566-2680 Fax
sbeall@aziyo.com

10.3 Possible Adverse Events

This study will capture events reported following the procedure and at follow up visits as reported by the PI and/or subject and from a review of medical records. The following device-related events have been identified as possible risks from the procedure:

- Allergic reaction to ECM
- Bleeding
- Calcification
- Fever
- Fibrosis
- Hematoma
- Infection
- Inflammation
- Seroma
- Undesired remodeling

There are no identified risks involved in participating in this post-market study.

11. Data Analysis

The primary endpoints are as follows:

1. The proportion of subjects with CanGaroo ECM related adverse events.
2. The incidence of major pocket infection.

Point estimates and exact 95% binomial confidence intervals will be provided for the true (population) values of these two endpoints.

The number and percentage of subjects with AEs and with device-related AEs will be presented by type of AE.

If possible, the rate of major pocket infection will be compared to the rate without use of the CanGaroo ECM device based on data from the U.S. Healthcare Cost and Utilization Project family of databases and/or contemporary literature.

Similarly, if possible, the rate of other AEs will be compared by type to the rate without use of the CanGaroo ECM device based on data from the U.S. Healthcare Cost and Utilization Project family of databases and/or contemporary literature.

12. Ethical Considerations

12.1 Code of Conduct

The Investigator will ensure that the clinical study is conducted in accordance with good clinical practice and all regulatory and institutional requirements, including those for subject privacy, informed consent, Institutional Review Board or Ethics Committee approval, and record retention. (Appendix D: Investigator Qualifications and Responsibilities)

Data quality will be monitored through review of submitted data to identify and follow up on missing data, inconsistent data, or incomplete data. Critical data points such as adverse events or infection will be reviewed with the site via telephone and/or email and if required, on-site monitoring will be conducted. All communication with the investigator and study staff related to monitoring and data collection will be documented per the Monitoring SOP. Monitoring and related activities will be performed by the Sponsor or its designee.

12.2 Ethics Committee / Institutional Review Board Approval and Oversight

The Investigator must obtain appropriate Ethics Committee ("EC") or Institutional Review Board ("IRB") approval before the study can be initiated. The Sponsor will submit the protocol and informed consent to a centralized IRB for approval. If the Investigator chooses to use the centralized IRB, the Investigator will be responsible for completing the initial review form for the Sponsor to submit on their behalf. If the investigator chooses to us their own IRB, the sponsor will provide support for the compilation and submission of the IRB package. A copy of the written approval from the EC/IRB and a copy of the approved Informed Consent Form (approved Waiver of Documentation of Consent, if applicable) should be sent to Aziyo. Appropriate study progress reports will be prepared for the EC/IRB by the Principal Investigator. Any changes to the protocol must be discussed and approved by Aziyo in writing unless the change is made to assure the safety of the subject. In the non-emergent setting, after agreement on the changes has been reached, an amendment to the protocol will be provided by Aziyo for submission to the EC/IRB for review and approval prior to initiation of the change. Any change made emergently must be documented in the

subject's medical record. The Investigator must immediately forward to the EC/IRB any written safety reports or updates from Aziyo.

12.3 Informed Consent and Subject Confidentiality

The Informed Consent/Waiver of Documentation of Consent and protocol must be approved by the local/centralized EC/IRB before the study is initiated and subjects enrolled. Prior to obtaining any study specific information approved informed consent will be reviewed with the subject and the subject must provide approval. Documentation of the consent process must be completed by the research personnel. The investigator shall provide a copy of the Informed Consent to the subject. Completed documentation of the consent process will be available for auditing by Aziyo or their representative, as applicable.

Aziyo will maintain the confidentiality of the identity of subjects enrolled in the study and the information contained in their study records. Aziyo will also instruct the study investigators in the importance of maintaining the confidentiality of study records. Any publication of any data collected as part of this trial will only use de-identified data, so that identification of any individual subject will not be possible. The records will be made available as required for review by the FDA, or other applicable regulatory agency and a reviewing IRB; however to the extent possible, the subject's identity will not be disclosed. The Case Report Forms will use a subject identification number, with the patient name and address NOT appearing anywhere on the study form to be submitted to the sponsor (Appendix E: Sponsor's Commitments).

13. Bibliography

Sundermann SH, Rodriguez Cetina Biefer H, Emmert MY, Falk V. Use of Extracellular Matrix Materials in Patients with Endocarditis. *Thorac Cardiovasc Surg.* 2014; 62(1):76-79.

Toyoda Y, Kashem MA, Hisamoto K, Shiose A Tricuspid valve reconstruction with the extracellular matrix tube technique: A word of caution. *J Thorac Cardiovasc Surg*. 2014; Epub ahead of print.

Deorsola L, Pace Napoleone C, Abbruzzese PA Repair of an unusual aortic coarctation using an extracellular matrix patch. *Ann Thorac Surg.* 2014; 97(3):1059-1061.

Szczeklik M, Gupta P, Amersey R, Lall KS Reconstruction of the Right Atrium and Superior Vena Cava with Extracellular Matrix *J Card Surg*. 2014

Zaidi AH, Nathan M, Emani S, Baird C, Del Nido PJ, Gauvreau K, Harris M, Sanders SP, Padera RF Preliminary experience with porcine intestinal submucosa (CorMatrix) for valve reconstruction in congenital heart disease: Histologic evaluation of explanted valves *J Thorac Cardiovasc Surg*. 2014;Epub ahead of print.

Yanagawa B, Rao V, Yau TM, Cusimano RJ Potential myocardial regeneration with CorMatrix ECM: A case report. *J Thorac Cardiovasc Surg*. 2014; Epub Ahead of Print.

Wallen J, Rao V Extensive Tricuspid Valve Repair After Endocarditis Using CorMatrix Extracellular Matrix *Ann Thorac Surg*. 2014;97(3):1048-1050.

Cua CL, Kollins K, McConnell PI Echocardiographic Analysis of an Extracellular Matrix Tricuspid Valve. *Echocardiography*. 2014

Slachman FN Constructive Remodeling of CorMatrix Extracellular Matrix After Aortic Root Repair in a 90-Year-Old Woman *Ann Thorac Surg*. 2014; 97(5):e129-e131.

Witt RG, Raff G, Van Gundy J, Rodgers-Ohlau M, Si MS Short-term experience of porcine small intestinal submucosa patches in paediatric cardiovascular surgery. *Eur J Cardiothorac Surg*. 2013; 44(1):72-76.

Eckhauser AW, Hannon D, Molitor M, Scaife E, Gruber PJ Repair of Traumatic Aortoinnominate Disruption Using CorMatrix. *Ann Thorac Surg*. 2013; 95(4):e99-e101.

Wyler von Ballmoos M, Murtaza G, Gasparri M, Masroor S. Reconstruction of the right atrium using an extracellular matrix patch in a patient with severe mediastinal aspergillosis. *Int J Surg Case Rep.* 2013; 4(3): 290-292.

Yeen WC, Faber C, Caldeira C, Nallamshetty L, Haddad T, Rolfe M Reconstruction of pulmonary venous conduit with CorMatrix in lung transplant. *Asian Cardiovasc Thorac Ann*. 2013;21(3):360-362.

Yanagawa B, Rao V, Yau TM, Cusimano RJ Initial Experience With Intraventricular Repair Using CorMatrix Extracellular Matrix. *Innovations (Phila)*. 2013; 8(5):348-352.

Stelly M, Stelly TC. Histology of CorMatrix Bioscaffold 5 Years After Pericardial Closure. *Ann Thorac Surg.*2013; 96(5):e127-e129.

Weber SS, Annenberg AJ, Wright CB, Braverman TS, Mesh CL. Early pseudoaneurysm degeneration in biologic extracellular matrix patch for carotid repair. *J Vasc Surg.* 2013; Epub ahead of print Gerdisch MW, Shea RJ, Barron MD

Gerdisch MW, Shea RJ, Barron MD Clinical experience with CorMatrix ECM in the surgical treatment of mitral valve disease*J Thorac Cardiovasc Surg*. 2013;Epub ahead of print.

Kalangos A, Myers PO Aortic cusp extension for surgical correction of rheumatic aortic valve insufficiency in children. *World J Pediatr Congenit Heart Surg*. 2013; 4(4):385-391.

Slachman FN. Constructive Remodeling of CorMatrix ECM Following Aortic Root Repair in a 90 Year-old Female.*Ann Thorac Surg.* 2013.

Dearani JA, Said SM, O'Leary PW, Burkhart HM, Barnes RD, Cetta F. Anatomic repair of Ebstein's malformation: lessons learned with cone reconstruction. *Ann Thorac Surg.* 2013; 95(1):220-6; discussion 226.

Poulin F, Horlick EM, David T, Woo A, Thavendiranathan P. 3-Dimensional transesophageal echocardiography-guided closure of a Gerbode shunt due to CorMatrix patch dehiscence. *J Am Coll Cardiol.* 2013; 62(3):e5.

Quarti A, Nardone S, Colaneri M, Santoro G, Pozzi M. Valve leaflet reconstruction in pediatrics with extracellular matrix patch. *J Heart Valve Dis.* 2012; 21(1):138-139.

Sundermann SH, Biefer HR, Emmert MY, Falk V. Use of Extracellular Matrix Materials in Patients with Endocarditis.*Thorac Cardiovasc Surg.* 2012;Epub ahead of print. DOI: 10.1055/s-0032-1328920

Smith CR, Stamou SC, Boeve TJ, Hooker RC. Repair of a penetrating ascending aortic ulcer with localized resection and extracellular matrix patch aortoplasty. *Ann Thorac Surg.* 2012; 94(3):988-989.

Chalajour F, Barboza LA, Boni L et al. Reconstruction of pulmonary artery in a newborn using a porcine small intestinal submucosal patch. *Ann Thorac Surg.* 2012; 93(4):1311-1315.

Mavroudis CD, Casillan A, Rabbat M et al. Primary Intimal Sarcoma of the Pulmonary Vein with Extension into the Left Atrium: A Case Report. *Open Journal of Thoracic Surgery.* 2012; 2(2):25-28.

Tweddell JS, Mitchell ME, Woods RK, Spray TL, Quintessenza JA. Construction of the Right Ventricle-to-Pulmonary Artery Conduit in the Norwood: The "Dunk" Technique. *Operative Techniques in Thoracic and Cardiovascular Surgery.* 2012; 17(2):81-98.

Boyd WD, Tyberg JV, Cox JL. A review of the current status of pericardial closure following cardiac surgery. *Expert Rev Cardiovasc Ther.* 2012; 10(9):1109-1118.

Quarti A, Nardone S, Colaneri M, Santoro G, Pozzi M. Preliminary experience in the use of an extracellular matrix to repair congenital heart diseases. *Interact Cardiovasc Thorac Surg.* 2011; 13(6):569-572.

Gerdisch MW, Akinwande AO, Matheny RG. Use of a novel acellular xenograft as a patch for aortic annular enlargement during aortic valve replacement. *Innovations.* 2010; 5(1):60-62.

Scholl FG, Boucek MM, Chan KC, Valdes-Cruz L, Perryman R. Preliminary experience with cardiac reconstruction using decellularized porcine extracellular matrix scaffold: human applications in congenital heart disease. *World Journal for Pediatric and Congenital Heart Surgery.* 2010; 1(1):132-136.

Boyd WD, Johnson WE, Sultan PK, Deering TF, Matheny RG. Pericardial reconstruction using an extracellular matrix implant correlates with reduced risk of postoperative atrial fibrillation in coronary artery bypass surgery patients. *Heart Surg Forum.* 2010; 13(5):E311-E316.

Piterina AV, Cloonan AJ, Meaney CL et al. ECM-based materials in cardiovascular applications: Inherent healing potential and augmentation of native regenerative processes. *Int J Mol Sci.* 2009; 10(10):4375-44

Appendix A

Sample Informed Consent

To be provided as a separate document

Appendix B

Case Report Form

To be provided as a separate document

Appendix C

Instructions for Use

To be provided as a separate document

Appendix D

Sponsor Commitments

SPONSOR'S COMMITMENTS

Aziyo is committed to:

1. Complying with the Declaration of Helsinki and all applicable health authority regulations governing the conduct of clinical research studies.
2. Protecting the rights, health, safety and welfare of study subjects.
3. Informing the clinical investigators of any new information about the study which may affect the health, safety, or welfare of the subjects, or may influence their decision to continue participation in the study.
4. Providing the clinical investigators with the study protocol and Case Report Form on which to document the study evaluation variables for each subject entered into the study.
5. Providing the clinical investigators and study staff training on the protocol and completion of the Case Report Form.
6. Providing the statistical analysis and study report writing resources necessary to complete reporting of the study results.
7. Certifying that EC/IRB approval of the protocol and Investigators Agreement will be completed prior to study initiation at a clinical site.

Appendix E

Investigator Qualifications and Responsibilities

INVESTIGATOR QUALIFICATIONS AND RESPONSIBILITIES

Each investigator must be a licensed physician who has received training for using the CanGaroo ECM®. The investigators have the following responsibilities:

1. **Subject Selection**

   The investigator is responsible for assuring that all subjects entering the study are eligible to participate.

2. **Informed Consent**

   The investigator is responsible for fully reviewing the nature of the study. The investigator is responsible for ensuring that Informed Consent is conducted by a qualified study team member in compliance with applicable regulations for each patient, prior to enrollment in the trial. A copy of the Informed Consent Form and documentation of the Informed Consent Process will be maintained in the patient's medical record.

3. **Ethics Committee (EC)/Institutional Review Board (IRB) Approval**

   The investigator must obtain approval for his participation in this protocol from an EC/IRB prior to entering any patients in the study. The Informed Consent document to be used will also be submitted by the Investigator or by qualified study team member to the EC/IRB for approval prior to initiation of the study. Assurance that the EC/IRB approval of the study protocol and Informed Consent has been obtained will be provided to the Sponsor prior to initiation of the study.

4. **Subject Evaluation and Data Reporting**

   The investigator is responsible for performing the patient evaluations or delegate to a qualified study team member, as described in the study protocol. All information generated by the patient evaluation will be recorded on the Case Report Form. Source documents will be maintained at the site.

5. **Record Retention**

   The Investigator or qualified study team member must retain all subject records for at least 2 years, or longer, if required by local regulations.