

POST-MARKET STUDY PLAN

Post-market study of the Biodesign® Hernia Graft

Clinical Study Number 19-004-CBI

Version: 19-004-01

Version Date: 05 November 2019

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I hereby acknowledge that the content presented in this Post-Market Study Plan has been reviewed and agreed upon.

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POST-MARKET STUDY PLAN SIGNATURE PAGE

Principal Investigator:

I hereby acknowledge that I have read and understand this Post-Market Study Plan and agree to comply with its content and requirements.

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CONFIDENTIALITY STATEMENT

This document shall be treated as a confidential document for the sole information and use of the clinical site personnel and the Institutional Review Board (IRB)

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1.0 Clinical Study Plan Overview

Objective:	To collect data on the performance of the Biodesign® Hernia Graft when used to reinforce soft tissues during ventral hernia repair.
Design:	Multicenter, open-label, prospective clinical study.
Primary performance endpoint:	Hernia recurrence through 1-year follow-up (hernia recurrence as defined in Appendix C).
Additional measures:	<p>The additional measures include summaries of the following:</p> <ul style="list-style-type: none">• Device-, procedure-, and hernia-related adverse event rates through the 2-year follow-up period• Hernia recurrence rate through 2-year follow-up• Operative times• Duration of hospital stay• Hospitalization times for related Serious Adverse Events (SAEs)• Patient-reported quality of life
Number of patients:	95 patients
Number of clinical sites:	5 clinical sites initially, with the possibility to add up to 5 more sites (for up to 10 clinical sites in total) as needed to mitigate enrollment difficulties or other unforeseen challenges.
Patient participation duration:	Patients will be followed at a minimum of 30 days, 6 months, 1 year, and 2 years post-procedure.
Expected study duration:	It is expected that enrollment will begin within 1 month of the first site being eligible to enroll. Individual patient enrollment will last through procedure and 2-year follow-up. Total study duration (from study initiation through patient enrollment and follow-up) is expected to be 5-6 years.

2.0 Ethical Considerations and Regulatory Compliance

This clinical study will be conducted in accordance with the Clinical Study Plan, the ethical principles that have their origin in the Declaration of Helsinki, ISO 14155, and other applicable local regulations as appropriate.

3.0 Objectives of the Clinical Study

The primary objective of this study is to collect data on the performance of the Biodesign Hernia Graft when used to reinforce soft tissues during ventral hernia repair.

The primary performance endpoint is the rate of hernia recurrence as defined in Appendix C through 1-year follow-up.

Additional objectives of this clinical study are to:

- Summarize the adverse event rates for normal commercial use of the device (e.g., seroma and infection rates)
- Assess the long-term success of the device in the reinforcement of hernia repairs through 2-year follow-up

Additional measures to address these objectives include summaries of the following:

- Device-, procedure-, and hernia-related adverse event rates through the 2-year follow-up period
- Hernia recurrence rate through 2-year follow-up
- Operative times
- Duration of hospital stay
- Patient-reported quality of life

4.0 Device Description

4.1 Intended Use (Europe)

The Biodesign® Hernia Graft is intended for implantation to reinforce soft tissues where weakness exists during ventral hernia repair.

4.2 Intended Use (rest of world)

The Biodesign® Hernia Graft is intended for implantation for to reinforce soft tissues where weakness exists. Indications for use include the repair of a hernia or body wall defect.

4.3 General Device Description

The Biodesign Hernia Graft is a graft composed of porcine small intestine submucosa (SIS). The device is CE-marked (G7 039164 0116) and cleared by the United States Food and Drug Administration (FDA) (K133306) for clinical use. The device will be used according to the labeled indication and in accordance with the Manufacturer's Instructions for Use (IFU).

The device IFU contains the following information:

- Instructions for storage and handling requirements
- Precautions and preparation for use of the device
- Description of the procedures involved in the use of the device including recommendations for device placement

4.4 Device Identification and Tracking

The Biodesign Hernia Graft is commercially available and will be obtained by each institution through normal commercial channels. Tracking of individual devices within the study will not be performed; however, information such as the size of each device used in a patient will be documented and recorded on electronic case report forms (eCRFs).

5.0 Background Information

The Biodesign Hernia Graft is comprised of 8 layers of decellularized porcine small intestinal submucosa (SIS) that has been pressed-lyophilized (i.e., freeze-dried under vacuum pressure) to laminate the component sheets (i.e., layers) together. In addition, it is perforated and sewn with 4-0 Trisorb suture (polyglycolic acid (PGA); Samyang Corporation, Seoul, South Korea). The suture is distributed in a diamond pattern across the graft and along the periphery and is intended to mitigate delamination of the layers upon rehydration and/or manipulation during implantation. Being a completely biologic device, the Biodesign Hernia Graft is considered MR safe.

The Biodesign Hernia Graft is available in eight (8) sizes: 8 cm x 10 cm, 8 cm x 20 cm, 8 cm x 30 cm, 10 cm x 10 cm, 13 cm x 15 cm, 13 cm x 22 cm, 20 cm x 20 cm, and 20 cm x 30 cm. The graft is terminally sterilized using an established ethylene oxide (EtO) sterilization cycle that has been validated to a sterility assurance level of 10^{-6} . Sterilization is routinely monitored, calibrated, and operated in adherence with standardized procedures. The Biodesign Hernia Graft may be stored at room temperature

in a clean, dry location for up to 18 months.

The Biodesign Hernia Graft is a technology that has been used in the treatment of hernias and abdominal wall defects for nearly 10 years. This post-market clinical follow-up study is being performed to confirm the continued safety and performance of the Biodesign Hernia Graft when used in accordance with its approved labeling.

6.0 Risk Analysis and Risk Assessment

6.1 Risks and Possible Adverse Reactions

Foreseeable adverse events associated with the use of the Biodesign Hernia Graft and other biologic graft prostheses are described in the IFU and will be collected in this study and reported as an additional measure.

Please reference the IFU for the following:

- Contraindications
- Warnings
- Precautions

The use of this FDA cleared device does not introduce any new or additional risk to standard ventral hernia procedures using biologic mesh materials.

Because the Biodesign Hernia Graft is cleared for general use in this patient population, the only additional patient risk associated with participation in this study is accidental release of protected health information.

6.2 Methods to Minimize Risks

In order to minimize the risks noted in the IFU, the procedure for proper use of the Biodesign Hernia Graft described in the IFU will be followed. In addition, only qualified surgeons with surgical training and experience in ventral hernia repairs will be involved in the study. Finally, the capture, handling, and storage of the study data are done in compliance with applicable regulations to minimize the risk of release of any personal health information.

6.3 Anticipated Clinical Benefits

There is no direct benefit for the patient regarding participation in this study, other than the benefit of having scheduled follow-up visits for two years to follow their general health status and outcome. However, it is important to gain more knowledge of the

performance of the Biodesign Hernia Graft in normal clinical use. The increased knowledge of the use of the product in this patient population will be beneficial for future patients and society as a whole.

7.0 Design of the Clinical Study

7.1 Design of the Clinical Study

This multicenter, open-label, prospective clinical study will evaluate the performance of the Biodesign Hernia Graft to reinforce soft tissues during ventral hernia repair.

This post-market study will enroll up to 95 patients at up to 10 clinical sites. Each clinical site will be limited to a maximum of 50 patients to ensure a variety of patients and surgical techniques are represented. There is no minimum enrollment number per site.

7.2 Study Design Rationale

This study has been designed as a multicenter, open-label, prospective study to collect data on the performance of the Biodesign Hernia Graft. The inclusion and exclusion criteria for this study have been selected based on the instructions outlined in the IFU so that the results from this study can provide data on the real world use of the device.

7.3 Duration of the Study and Patient Participation

Patient enrollment is expected to be completed within 3-4 years of study initiation. Total study duration (from study initiation through patient enrollment and follow-up) is expected to be 5-6 years.

Patients are expected to participate in this study for 2 years (\pm 90 days) after the study procedure.

7.4 Measures to be Taken to Avoid or Minimize Bias

This multi-center, open-label, prospective study is intended to collect information regarding the performance of the study device. Patients will be selected and included in accordance with the eligibility criteria and the need for a biologic graft to treat their hernia. In addition, the study will utilize uniform definitions for study endpoints. Study results will be analyzed in accordance with the prospectively defined analysis plan outlined in Section 11.

7.5 Endpoints

7.5.1 Primary Endpoint

The primary performance endpoint is the rate of hernia recurrence as defined in Appendix C through 1-year follow-up.

7.5.2 Additional Measures

Additional measures will include the following:

- Device-, procedure-, and hernia-related adverse event rates through the 2-year follow-up period
- Hernia recurrence rate through 2-year follow-up
- Operative times
- Duration of hospital stay
- Hospitalization times for related SAEs
- Patient-reported quality of life

7.5.3 Rationale for Endpoints

The endpoints and measures were chosen since hernia recurrence and adverse events related to the use of surgical grafts have been identified as issues of clinical interest; many of these events often result in additional surgical procedures. Furthermore, patient quality of life has been chosen as an additional measure to capture the outcome of the intervention from the patient's perspective. Using patient-reported outcomes measures, we will be able to evaluate abdominal wall function and patient's perception of pain independently of hernia recurrence.

7.6 Variables to be Measured to Demonstrate Achievement of Endpoints

The endpoints and measures will be assessed as described in Table 7.6-1.

Table 7.6-1. Assessment of Endpoints and Measures

Endpoint / Measure	Assessment ¹
Hernia recurrence	Clinical examination
Rate of adverse events	Evaluation based upon reports of events submitted by the study sites
Rate of Surgical Site Occurrences (SSO)	Evaluation based upon reports of occurrences submitted by the study sites
Rate of Surgical Site Occurrences needing Intervention (SSOPI)	Evaluation based upon reports of occurrences submitted by the study sites

Patient quality of life	Postoperative assessment (patient questionnaire)
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¹For the 1 and 2-year follow-up visits: Every attempt should be made to have the patient return for a physical exam at the 1-year and 2-year timepoints in order to determine hernia recurrence. Results from a physical exam made by a non-study physician (e.g. primary care physician) can be included if assessment at the clinical site is not possible.

If the patient refuses or is unable to return in person for the 1-year or 2-year physical exam, patient self-assessment of the presence of recurrence symptoms, patient responses regarding adverse events, and patient questionnaires may be obtained via telephone or email. If the patient self-assessment of the presence of recurrence symptoms suggests that a hernia is present, the patient should be contacted and requested to return for a physical exam for confirmation.

Patient reported outcomes will be tabulated and reported. The primary endpoint will be analysed as noted in Section 11.0.

Patient data will be documented by trained personnel at the clinical site and recorded onto eCRFs through an electronic data capturing (EDC) system. The assessment schedule is summarized in Table 7.6-2 and in Appendix B:

Table 7.6-2. Assessment schedule

	Pre-Procedure	Procedure	Follow-up			
			30 days (± 15 days)	6 month (± 30 days)	1 year (± 90 days)	2 years (± 90 days)
Consent	X					
Medical history	X					
Procedure Information		X				
Physical exam	X	X	X	X	X	X
Patient Reported Outcomes measures			X	X	X ^a	X ^a
Adverse events		X	X	X	X ^a	X ^a

^a Every attempt should be made to have the patient return for a physical exam at the 1-year and 2-year timepoints in order to determine hernia recurrence. Results from a physical exam made by a non-study physician (e.g. primary care physician) can be included if assessment at the clinical site is not possible. If the patient refuses or is unable to return in person for the 1-year or 2-year physical exam, patient

self-assessment of the presence of recurrence symptoms, patient responses regarding adverse events, and patient questionnaires may be obtained via telephone or email.

8.0 Eligibility Criteria

Patients will be selected in accordance with the device's labeled indication and according to the Manufacturer's Instructions for Use.

Inclusion Criteria

Patients who meet the following criterion are suitable for receiving a Biodesign Hernia Graft, and are therefore suitable for inclusion in this study:

1. Primary or recurrent ventral hernia in need of surgical repair

Exclusion Criteria

According to the IFU, the Biodesign Hernia Graft should not be used in patients with known sensitivity to porcine material. Therefore, the following patients will be excluded from the study:

1. Known sensitivity to porcine material

For the purpose of the study, the following patients will also be excluded:

2. Age < 18 years
3. Unable or unwilling to provide informed consent
4. Life expectancy of less than one year from the date of the index procedure

Patients will be excluded from the study if they never receive a Biodesign Hernia Graft during their index procedure.

8.1 Patient Consent

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be invited to participate in this study. Patients eligible for enrollment will have the clinical study explained to them, as well as the potential risks and benefits of their participation in the study, at a time point sufficiently prior to study participation to allow the patient adequate time to fully consider their participation in the study. All information pertinent to the study will be provided in writing in a language understandable to the patient. Each patient who decides to participate will sign and date an informed consent document prior to the procedure or any study-specific assessments. If new information is obtained, patients who have not exited the study will be informed about the new information, and will be re-consented if required by the clinical site's IRB.

9.0 Methods

9.1 Pre-procedure Evaluation

Prior to patient enrollment, patients will undergo a baseline evaluation. Assessments will be completed as described in Table 9.1-1. All pre-procedure assessments are considered standard of care.

Table 9.1-1. Pre-procedure requirements

Pre-procedure	
Timing	Prior to the study procedure
Type	In-person
Assessment	Review study with patient and obtain written informed consent
	Clinical assessment including hernia assessment and symptomology
	Record patient demographics and pre-op evaluation

9.2 Point of Enrollment

Patients are considered enrolled in the study when the device implant procedure is completed.

9.3 Study Procedure

The patient will undergo repair of a ventral hernia with the implantation of the Biodesign Hernia Graft, and any other concomitant procedures that are clinically indicated. Presence of hernia will be confirmed intra-operatively and classified using the European Hernia Classification System.

The device will be implanted according to the IFU.

Peri- and post-operative patient treatment will be conducted in accordance with surgeon discretion and institutional standard of care. All peri- and post-operative details will be documented and recorded on the eCRFs within the EDC system.

Discharge following the procedure will be in accordance with surgeon discretion and institutional standard of care. Patients should be given instructions to refrain from activity that may complicate recovery.

9.4 Follow-up

Patients are expected to participate in this study for 2 years after the procedure. The follow-up visits will occur within the time frames listed below. Following the study procedure, assessments will be completed as described in Table 9.4-1.

Table 9.4-1. Follow-up requirements

30-day Follow-up (± 15 days)	
Timing	15-45 days following the study procedure
Type	In person
Assessments	Physical exam of the incision and abdominal wall
	Record specific data points within the EDC system
	Administer a postoperative assessment (patient questionnaire)
6- month Follow-up (± 30 days)	
Timing	153-213 days following the study procedure
Type	In person
Assessments	Physical exam of the incision and abdominal wall
	Record specific data points within the EDC system
	Administer postoperative assessment (patient questionnaire)
1-Year Follow-up (± 90 days)	
Timing	275 – 455 days following the study procedure
Type	In person ¹
Assessments	Physical exam of the incision and abdominal wall
	Record specific data points within the EDC system
	Administer postoperative assessment (patient questionnaire)
2-Year Follow-up (± 90 days)	
Timing	640 – 820 days following the study procedure
Type	In person ¹
Assessments	Physical exam of the incision and abdominal wall
	Record specific data points within the EDC system
	Administer postoperative assessment (patient questionnaire)

¹For the 1 and 2-year follow-up visits: Every attempt should be made to have the patient return for a physical exam at the 1-year and 2-year timepoints in order to determine hernia recurrence. Results from a physical exam made by a non-study physician (e.g. primary care physician) can be included if assessment at the clinical site is not possible.

If the patient refuses or is unable to return in person for the 1-year or 2-year physical exam, patient self-assessment of the presence of recurrence symptoms, patient responses regarding adverse events,

and patient questionnaires may be obtained from the patient via telephone or email. If the patient self-assessment of the presence of recurrence symptoms suggests that a hernia is present, the patient should be contacted and requested to return for a physical exam for confirmation.

Patient reported outcomes will be tabulated and reported. The primary endpoint will be analysed as noted in Section 11.0.

9.5 Adverse Events

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects (patients), users, or other persons, whether or not related to the medical device.

A Serious Adverse Event is an adverse event that:

- Led to death,
- Led to serious deterioration in the health of the subject (patient), 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.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the study plan, without serious deterioration in health, is not considered a serious adverse event.

The EDC system allows for recording of adverse events and should therefore be used as the typical method of adverse event reporting. The study sponsor will periodically review adverse events that have been added to the EDC system and will process these events according to standard operating procedures. If an adverse event meets the criteria for reporting to a regulatory agency, the sponsor will contact the principal investigator and will perform a thorough investigation of the adverse event as required under applicable regulations. The sponsor is responsible for reporting events to the regulatory authorities, the reviewing IRB(s), and the principal investigator(s), as required according to applicable regulations/standards/policies.

Serious Adverse Events should be added to the EDC system and reported to the study sponsor within 3 calendar days of the study site becoming aware of the event.

The principal investigator will notify their IRB of applicable adverse events occurring for the duration of the study according to institutional guidelines.

10.0 Participation Endpoints of the Study

A patient's participation in the study will end after any of the following:

- Completion of all scheduled clinical evaluations through 2 years
- Subsequent procedure due to recurrence of the original hernia defect
- Any subsequent surgical procedure resulting in removal of the study device
- Patient withdrawal
- Principal investigator withdrawal of patient
- Patient loss to follow-up
- Patient death

After a patient exits the study for any reason, there are no study-specific requirements for follow-up and no additional data will be collected. Any data collected up to the point of patient exit may be used in the study.

10.1 Patient Withdrawal

A patient may decide to withdraw from the study at any time either before or after undergoing the study procedure without prejudice or loss of care. The principal investigator may also decide to withdraw the patient from the study at any time based on medical judgment. The principal investigator will ensure that the sponsor is notified of any patient withdrawal. In all instances of withdrawal, data collected up to the time of patient withdrawal, will be submitted and will include the reason why the patient has been withdrawn from the study (e.g. patient request).

10.2 Patient Loss to Follow-up

In the event a patient cannot be reached for post-procedure assessments, at least three attempts will be made to contact the patient; efforts (and methods) to contact the patient will be documented. If the patient cannot be located and is determined to be unreachable, data collected up to the time of patient loss to follow-up will be submitted.

10.3 Early Termination or Suspension of the Clinical Study

Any decision to suspend enrollment or terminate the clinical study, either completely or at one or more clinical sites, will be made by the sponsor or the IRB. Reasons for early termination or suspension of a study (at one or more sites) may be due to ethical concerns, clinical site performance, or organizational issues. In the event of clinical site

or study closure, all patients who have received the study treatment will be followed until their primary endpoint is met.

The sponsor is responsible for reporting early termination or suspension of the study to the IRB(s) and principal investigators as required according to applicable regulations and standards.

11.0 Statistical Considerations

11.1 Sample Size

A sample size of 86 patients was determined using a confidence interval-based approach with the following assumptions:

- 80.1% success (freedom from hernia recurrence) at 1 year, based on recurrence rates for biologic meshes from literature review (Table 11.1-1).
- $\alpha = 0.05$, power = 0.8, margin = 10%
- 2-sided confidence interval

To account for patients lost to follow-up, this study intends to enroll 95 patients.

Table 11.1-1. Summary of Review Data on the Use of Biologic Graft for Ventral Hernia Repair

Paper	Mesh	Length of Follow up	Recurrence - pooled rate (n)	Infection Complications - pooled rate (n)
<i>Clean/Clean Contaminated</i>				
Darehzereshki A, et al., <i>World J Surg.</i> 2014	Biologic	14.7-66 mo	18.6% (311)	10.9% (155)
	Synthetic	13-66 mo	15.7% (533)	36.5% (85)
Lee L, et al., <i>Surg Endosc.</i> 2014	Biologic	Most > 1yr	12.5% (214)	31.6% (214)
	Synthetic	Most > 1yr	8.2% (434)	6.4% (434)
Fischer J et al., <i>Plast Reconstr Surg.</i> 2016	Biologic	12-32.9 mo	14.6% (159)	32.1% (159)
	Synthetic	12-39 mo	17.6% (135)	19.1% (135)
<i>Clean Contaminated or Potentially Contaminated[#]</i>				
Atema J et al., <i>Am J Surg.</i> 2016	Biologic	12-26.4 mo	9% (807)	21% (807)
	Synthetic	13.1-36 mo	9% (204)	12% (204)
<i>Contaminated, Dirty or Infected</i>				
Cross W et al., <i>Am Surg.</i> 2014	Biologic	5.8-52 mo	20% (554)	24% (554)
Lee L, et al., <i>Surg Endosc.</i> 2014	Biologic	Most > 1 yr	27.2% (549)	35.5% (582)
	Synthetic	Most > 1yr	3.2% (74)	42.6% (74)
Atema J et al., <i>Am J Surg.</i> 2016	Biologic	14-26 mo	30% (527)	38% (527)
	Synthetic*	10.8 mo	7% (100)	11% (100)
	Biologic	4.5 –29 mo	25.8% (357)	Not Provided

Hodgkinson J et al., <i>Colorectal Dis.</i> 2017	Synthetic	14 – 74 mo	29% (131)	Not Provided
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Atema et al. grouped clean contaminated and potentially contaminated cases together in the review paper

* Results from a single study (review was only able to identify one study on use of synthetics in contaminated fields)

11.2 Analyses

Patients' baseline medical characteristics will be summarized. For continuous baseline characteristic variables, descriptive statistics will be provided; for categorical baseline characteristic variables, contingency tables will be tabulated to display the distribution.

The primary endpoint is the rate of hernia recurrence as defined in Appendix C through 1-year follow-up. Patients whose device is damaged in a subsequent procedure prior to reaching the primary efficacy endpoint will not be included in the primary endpoint analysis. The point estimate and the 95% confidence interval will be summarized.

11.3 Hypothesis to be Tested

The primary hypothesis for effectiveness is the rate of hernia recurrence through 1-year follow-up (π_{graft}). The null (H_0) and alternative (H_A) hypotheses for the primary effectiveness are expressed as follows:

$$H_0 : \pi_{graft} \geq 22\%$$

$$H_A : \pi_{graft} < 22\%$$

11.4 Planned Subgroups and Covariates

All patients enrolled in the study, except patients whose device is damaged in a subsequent procedure prior to reaching the primary efficacy endpoint, will be included for the primary analyses. If warranted, baseline characteristics (including but not limited to: patient demographics and hernia type) and procedural details (including but not limited to: procedure type (laparoscopic or open), surgical repair technique, fascial closure, and location of device placement) will be analyzed to determine their impact on the hernia recurrence rate.

11.5 Missing Data

The total study enrollment is augmented to achieve sufficient data to analyze the study outcome in the presence of missing data due to lost to follow-up or withdrawn patients. However, it is also recognized that patients may refuse or be unable to return to the study

site for a physical exam at the 1-year and 2-year timepoints, leading to missing physical exam information.

The primary endpoint will be analyzed using per-protocol and analyzable patient populations to assess the robustness of the efficacy results. Three imputation methods will be implemented for missing physical exam data to evaluate the impact of missing data on the conclusions of treatment effect: (1) complete case analysis, (2) estimating missing data with the best available data, (3) multiple imputation. All three methods for missing data will be used to assess the robustness of the primary endpoint.

Analyses will account for missing data in the following manner: if missing data can be determined from a subset of best available data, these data will be documented and analyzed. Multiple imputation will be considered, and appropriate methods to impute data based on the analysis population will be documented and presented in the analysis results.

Specifically, when dealing with missing physical exam information for the primary recurrence endpoint, the following analysis is planned:

1. Patients self-reporting the absence of recurrence symptoms will be deemed to not have experienced a hernia recurrence in the absence of physical exam/imaging information.
2. Data from patients with both physical exam/imaging information and positive recurrence symptoms on the self-assessment will be utilized to assess the accuracy of patient self-reporting of hernia recurrence.
3. This level of accuracy will be applied to the patient subset with only positive recurrence symptoms on the self-assessment as a means of estimating the true recurrence rate.

11.6 Site-level Poolability

Poolability of data from multiple clinical sites will be verified by examining the primary endpoint across sites. Site-level poolability will be considered appropriate provided that the endpoint is similar across clinical sites.

It is expected that some clinical sites may have too few patients to provide reasonable site-level estimates of the primary measure. Pooling of this information will be explored based on relevant covariates such as: hospital size (e.g. number of beds, number of annual discharges), clinical site enrollment, type of hospital (community versus teaching), and geographic region.

It is recognized that patient baseline characteristics may differ across clinical sites, with some clinical sites routinely treating patients with more severe disease progression. It is anticipated that the primary endpoint measure may be related to covariates that reflect this disease progression, which are in turn related to outcome. Thus, observed site-specific differences among the primary endpoint may be checked for confounding with other measured covariates (e.g., age, sex). This can be accomplished using regression models (linear and logistic where appropriate) that include clinical site and other measured covariates as independent variables.

Should one or more clinical site(s) be found to differ significantly from the rest, then subsequent analyses may include the discriminating covariate or a covariate to distinguish between the unusual clinical site(s) and those clinical sites that are considered poolable.

11.7 Limitations of the Study

A limitation of this study is that it includes patients regardless of concomitant diseases and medications. This can introduce a potential heterogeneity that potentially can compromise the outcome of the study. Another limitation of this study is that it allows for the hernia repair procedure to be conducted using open, laparoscopic and/or robotic techniques, and allows for both acute and elective repairs. The rates of adverse events and hernia recurrences may differ across repair types and techniques, which introduces a possible bias. On the other hand, the inclusion of patients regardless of concomitant diseases and medications and regardless of type of repair or technique reflects a more diverse population and provides more real-world data.

12.0 Deviations from Clinical Study Plan

Except under emergency situations when necessary to preserve the rights, safety, or well-being of study patients, principal investigators are not allowed to deviate from this protocol without documented prior approval by the sponsor and the IRB. Clinical study noncompliances (i.e., deviations from the protocol, investigator agreement, IRB policy, and/or any applicable regulations) will be documented, along with an explanation.

Deviations or non-compliances that impact the rights, welfare, or safety of patients will be reported to the sponsor and IRB as required and as soon as possible. If appropriate, corrective and preventive actions will be discussed by the sponsor, investigator, and/or the IRB to determine a suitable course of action.

The sponsor is responsible for reporting clinical study noncompliances to the reviewing IRB(s) and investigator(s) as required according to applicable regulations and standards.

In accordance with applicable regulations/standards, the sponsor will review all clinical study noncompliances and take suitable action(s) to secure compliance. If appropriate, based on the number and nature of noncompliances, actions may include termination of a principal investigator's participation in this clinical study.

13.0 Data Collection and Management

Patient data will be documented and recorded by trained personnel at the clinical site onto eCRFs through an EDC system. This is a secure, validated, web-based system, allowing those with permission to access data from any location at any time. Source data will be retained for all data entered into the EDC system. In cases where patient responses regarding hernia symptoms, adverse events, and/or questionnaires are obtained by telephone, the data provided from the telephone interview may be entered directly into the EDC system and will be considered source data.

Clinical site personnel are required to undergo training and will have unique login names and passwords in order to enter patient data. The EDC system creates a secure, computer-generated, time stamped audit trail to record the date and time of operator entries and actions that create, modify, or delete electronic records. Principal investigators shall review and electronically sign the eCRFs to confirm that the data recorded are accurate and complete.

Principal investigators will input all applicable clinical data and documentation into the EDC system in a timely manner. All clinical study documents (including patient data) will be retained at the study sites as required by the applicable regulations and standards. The principal investigator or clinical site personnel should contact the sponsor before removing any documents pertaining to the clinical study (i.e., patient consent forms).

The Sponsor is responsible for data management, data verification, data archiving, and data retention.

As needed to assist the sponsor in its research (e.g., during evaluation of an adverse event), data will be accessible to the sponsor, the participating principal investigators, the manufacturer, and companies or individuals the sponsor authorizes.

14.0 Monitoring

The conduct of the clinical study will be supervised through a process of centralized and on-site monitoring.

For the first 2 patients at each study site, the electronic data entries in the EDC system will be checked for accuracy to the medical record. If the data accuracy check demonstrates that the site is accurately (90% compliance with data fields) entering the data into the EDC system, no additional monitoring of the site will be required. If the data accuracy check reveals deficiencies that call into question the inputted data, the sponsor will arrange for more formal on-site monitoring to occur.

A formal query process in the EDC system will be utilized to resolve data discrepancies. Queries may arise from automated processes or from manual review of eCRFs, procedural reports, or correspondence received. Principal investigators will ensure timely resolution of queries.

On-site monitoring will be implemented as necessary throughout the course of the study to ensure the principal investigators are fulfilling the obligations set forth in the CIP, agreement(s), IRB policies, and applicable regulations and standards. Source data verification will be performed during these on-site visits. The principal investigator and clinical site will provide direct access to source data and documents for study-related monitoring, audits and IRB review.

15.0 Clinical Study Administration

15.1 Approvals

The principal investigator is responsible for obtaining approval of this clinical study (including the CIP, informed consent form, and all patient materials) from the relevant IRB at their associated clinical site. The clinical study will not begin at a particular clinical site until a favorable opinion of the IRB has been obtained. The protocol and other clinical study documents may be revised by the sponsor, as appropriate, based on new or changes to important information. Changes or modifications to the protocol, informed consent form, or patient materials will not be initiated without IRB approval. The principal investigator is responsible for keeping their IRB informed as to the progress of the study and complying with requirements imposed by their IRB and/or regulatory authority. Furthermore, the sponsor and the principal investigator will ensure that local regulations concerning data protection are followed.

15.2 Clinical Study Reporting

Principal investigators will provide notifications to the sponsor within 5 working days of withdrawal of IRB approval. The sponsor is responsible for providing progress reports and final reports, notification of study completion or termination to IRB(s) and principal

investigator(s) as required according to applicable regulations and standards. Furthermore, the sponsor is responsible to report any changes significantly affecting the conduct of the clinical study and/or increasing risk to the patient to the IRB(s).

15.3 Contact Information

Refer to Appendix A for a list of the sponsor, monitor, and the manufacturer.

Contact information and qualifications for the clinical site(s), principal investigator(s), co-investigators or other institutions involved, will be maintained by the sponsor. The sponsor will also maintain contact information for each IRB.

15.4 Insurance

The device is covered by the sponsor's product liability insurance. A clinical study insurance policy will be taken out according to local requirements.

16.0 Publication Policy

This clinical study will be registered on www.ClinicalTrials.gov and the intent is to make study results public. Publication policy, rights, and obligations for this study will be negotiated, detailed and defined in the clinical study's contractual documents with the clinical site and principal investigator.

17.0 References

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2. Bellows CF, Smith A, Malsbury J, et.al. Repair of incisional hernias with biological prosthesis: a systematic review of current evidence. *Am J Surg.* 2013; 205(1):85-101.
3. Beale EW, Hoxworth RE, Livingston EH, et.al. The role of biologic mesh in abdominal wall reconstruction: a systematic review of the current literature. *Am J Surg.* 2012;204(4):510-517.
4. Lee L, Mata J, Landry T, et al. A systematic review of synthetic and biologic materials for abdominal wall reinforcement in contaminated fields. *Surg Endosc.* 2014;28(9):2531-2546.
5. El-Hayek K, Yoo J, Phillips M, et.al. Zenapro™ Hybrid Hernia Repair Device for Ventral Hernia Repair. Abstract presented at: *1st World Conference on Abdominal Wall Hernia Surgery*; April 2015; in Milan; Italy.

6. El-Hayek K, Yoo J, Phillips M, et.al. First Human Experience with a Hybrid Biologic and Synthetic Mesh: Zenapro™ Hernia Repair Device for Ventral Hernia Repair. Abstract presented at: *Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Annual Meeting*; March 2016; Boston, MA; US.
7. Muysoms FE, Miserez M, Berrevoet F, et.al. Classification of primary and incisional abdominal wall hernias; *Hernia*. 2009; 13(4):407-14.
8. The Ventral Hernia Working Group: Breuing K, Butler CE, Ferzoco S, et.al. Incisional ventral hernias: Review of the literature and recommendations regarding the grading and technique of repair; *Surgery* 2010;148:544-58.

APPENDIX A: Contact Information

Global Sponsor and Monitor

Cook Biotech Incorporated
1425 Innovation Place
West Lafayette, IN 47906
USA

Contact: Samantha Stevenson
Clinical Project Manager
Telephone: +1-765-497-3355
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Manufacturer

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1425 Innovation Place
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Contact: Jason Hodde
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Telephone: +1-765-497-3355
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APPENDIX B: Study Event Schedule

	Pre-Procedure	Procedure	Follow-up			
			30 days (± 15 days)	6 months (± 30 days)	12 months (± 90 days)	2 years (± 90 days)
Informed consent	X					
Medical history	X					
Procedure Information		X				
Physical exam	X	X	X	X	X ¹	X ¹
Patient Reported Outcomes measures			X	X	X ¹	X ¹
Adverse events		X	X	X	X ¹	X ¹

¹Every attempt should be made to have the patient return for a physical exam at the 1-year and 2-year timepoints in order to determine hernia recurrence. Results from a physical exam made by a non-study physician (e.g. primary care physician) can be included if assessment at the clinical site is not possible. If the patient refuses or is unable to return in person for the 1-year or 2-year physical exam, patient self-assessment of the presence of recurrence symptoms, patient responses regarding adverse events, and patient questionnaires may be obtained via telephone or email.

APPENDIX C: Definitions

Center of Disease Control (CDC) Wound Classification:

Classification	Description
Clean (Class I)	An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow non-penetrating (blunt) trauma should be included in this category if they meet the criteria.
Clean-contaminated (Class II)	An operative wound in which the respiratory, alimentary, genital, or urinary tract are entered under controlled conditions and without unusual contamination. Specifically, operations including the biliary tract, appendix, vagina, and oropharynx are included in this category provided no evidence of infection or major break in sterile technique is encountered.
Contaminated (Class III)	Open, fresh, accidental wounds. In addition, operations with a major break in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute nonpurulent inflammation is encountered are included in this category.
Dirty-infected (Class IV)	Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing post-operative infection were present in the operative field before the operation.

Hernia Recurrence (recurrence of tissue defect):

Any of the following post-operative findings at the site of the hernia defect repaired at the index procedure will be categorized as a hernia recurrence:

- A symptomatic, palpable or visible protrusion of underlying tissue through a defect in the abdominal wall, possibly with a palpable fascial defect

Any patient who presents asymptotically, but additional imaging indicates presence of a hernia.