CLINICAL STUDY PROTOCOL

Title:	**A Post-Market, Prospective, Multi-Center, Single-Arm Clinical Investigation of Phasix™ Mesh for VHWG Grade 3 Midline Hernia Repair**
Protocol Number:	**DVL-HE-016**
Study Type:	**Post-market, prospective, single arm, multi-center, open-label study (N=85)**
Date:	**12 Oct 2018**
Version:	**2.0**
Study Devices:	**Phasix™ Mesh**
Sponsor:	**Davol Inc.** **Subsidiary of C. R. Bard, Inc.** **100 Crossings Boulevard** **Warwick, RI 02886, USA** **Phone: +1-800-556-6756**
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Protocol Signature Page

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision and the relevant Ethics Committee. I will discuss this material with them and ensure they are fully informed regarding the conduct of the study according to ISO 14155:2011, the Declaration of Helsinki in its currently recognized version, and any national and local regulations.

Agreed to by (Investigator):

_____
Printed Name – Investigator

_____
Signature – Investigator

_____
Date

Phasix Mesh™ Protocol Summary

Title	A Post-Market, Prospective, Multi-Center, Single-Arm Clinical Investigation of Phasix™ Mesh for VHWG Grade 3 Midline Hernia Repair
Study Device	Phasix™ Mesh
Study Design	Post-market, prospective, single-arm, multicenter, open-label study (N=85).
Region	Europe
Patient Population	Ventral Hernia Working Group (VHWG) Grade 3 midline hernia patients. Grade 3 (potentially contaminated) includes the presence of a nearby stoma, bowel resection, violation of the gastrointestinal tract, or history of wound infection.
Overview	Approximately 85 subjects, at approximately 12 sites across Europe will be enrolled and treated to study the use of Phasix™ Mesh. All treated subjects will be followed for 2 years post-implantation.
Purpose	The plan is to study the use of Phasix™ Mesh in VHWG Grade 3 midline hernia patients.
Objective	The objective of this study is to collect additional data on safety and performance of Phasix™ Mesh in subjects requiring VHWG Grade 3 midline hernia repair.
Enrollment	85 patients treated with Phasix™ Mesh at 12 clinical sites Estimated recruitment time: 15 months Estimated recruitment time + complete 2 years follow up visits: 39 months
Subject Follow-Up Schedule	Follow-up visits will be conducted at drain removal (per standard of care, SOC), 1, 3, 6, 12, 18, and 24 months following surgery.
Safety Review	From the date of Phasix™ Mesh implant to each subject's 3 month assessment visit, the following safety reassessment applies: Greater than 4 device-related SAEs or greater than 1 device-related recurrence. If the criteria for reassessment are met: 1. Enrollment and implantations are suspended until the impact of the study parameters (e.g., surgical technique, hernia size/mesh size, protocol deviations (if any), AE time-course) on the results is assessed by the safety committee 2. The follow-up for the subjects already treated continues
Primary Endpoint	**Surgical Site Occurrence (SSO) rate up to (including) the 3-month (± 14 days) Follow-Up Assessment:** Occurrences at the surgical site will be assessed by physical examination at each study visit through 3 months (± 14 days). Surgical site occurrence will be defined as hematoma, seroma, surgical site infection, wound dehiscence, skin necrosis and fistula requiring intervention.
Secondary Endpoints	1. Surgical Site Occurrence (SSO) rate > 3-month follow-up assessment 2. Hernia Recurrence Rate (via physical exam, if uncertain via ultrasonography, if uncertain, via CT/MRI). 3. Surgical Site Infection rate 4. Pain - Visual Analog Scale (VAS) 5. Device-related adverse event incidence 6. Rate of reoperation due to the index hernia repair 7. Quality of life assessments (Carolinas Comfort Scale® and EQ-5D™) 8. Surgical procedure time as measured from incision to closure (skin to skin)

	9. Return to Work 10. Length of stay in hospital (day of index surgery until day of discharge, LOS)
Inclusion Criteria	1. Subject must be 18 years of age or older. 2. Subject must be diagnosed with incisional midline hernia. 3. Subject has a VHWG Grade 3 hernia (as defined in the protocol). 4. Size of hernia $\geq$ 10 cm^2. 5. Subject must be willing to undergo a planned retro-rectus hernia repair (onlay allowed as an exception when retro-rectus placement cannot be achieved; using absorbable suture) with or without Component Separation Technique (CST). 6. The subject is legally competent, has been informed of the nature, the scope and the relevance of the study, voluntarily agrees to participation and the study's provisions, and has duly signed the informed consent form (ICF). Subject agrees to comply with the protocol-mandated procedures and visits.
Exclusion Criteria	1. Subject with > 4 previous repairs of the hernia under observation. 2. Body Mass Index (BMI) > 35 kg/m^2. 3. The subject is on, or suspected to be placed on, chemotherapy medications during any part of the study. 4. The subject has peritonitis. 5. Known human immunodeficiency virus (HIV) infection (if documented in the subject's record). 6. The subject has cirrhosis of the liver and/or ascites. 7. Subject is American Society of Anesthesiology Class 4 or 5. 8. Complete removal of existing mesh from a prior hernia repair (in the same affected area) is not possible. 9. The hernia repair requires more than a single piece mesh (with adequate overlap beyond the margins of the defect on all sides). 10. Subject has intact permanent mesh adjacent to the current hernia to be repaired. 11. Subject's hernia repair requires intraabdominal mesh placement. 12. Surgical technique requires surgical bridge repair as the sole repair. 13. Subject has any condition that, in the opinion of the Investigator, would preclude the use of the study device, or preclude the subject from completing the follow-up requirements. 14. Subject is pregnant or has plans to become pregnant during the study period or is currently breastfeeding. 15. Subject has an alcohol/substance abuse problem or has had a relapse within 12 months of the screening visit. 16. Subject was involved in another interventional clinical study in the last 30 days prior to ICF signature. 17. Subject is part of the site personnel directly involved with this study. 18. Subject has a life expectancy of less than 2 years at the time of enrollment. 19. Subject has a known sensitivity to Phasix™ Mesh or component materials (patients with known allergies to tetracycline hydrochloride or kanamycin sulfate should be avoided).
Primary Analysis Subset	Modified intention-to-treat (mITT) population which is defined as all subjects in whom Phasix Mesh has been implanted.

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Protocol Abbreviations/Acronyms

Abbreviation/Acronym	Definition
ADE	Adverse Device Effect
AE	Adverse event
Bard	C. R. Bard, Inc.
BMI	Body Mass Index
CAD	Coronary Artery Disease
CBGB	Coronary artery bypass graft with both chest and donor site incisions
CCS	Carolina Comfort Scale
CDC	US Centers for Disease Control and Prevention
CE	Conformité Européenne
CIP	Clinical Investigational Plan
cm	Centimeter
COPD	Chronic Obstructive Pulmonary Disease
CRO	Clinical Research Organization
CST	Component Separation Technique
CT	Computed Tomography Scan
CV	Curriculum vitae
DIP	Deep Incisional Primary
DIS	Deep Incisional Secondary
DM	Diabetes Mellitus
DMP	Data Management Plan
e.g.	For Example
early term. /ET	Early Termination Visit
eCRF	Electronic Case Report Form
EEA	European Economic Area
EEC	European Economic Community
EQ-5D	EuroQol 5 Dimensions
etc.	Et Cetera.
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HIV	Human Immunodeficiency Virus
Hrs	Hours
i.e.	That Is
ICF	Informed Consent Form
IFU	Instructions For Use
Inc.	Incorporated
ISO	International Organization for Standardization
ITT	Intention-to-treat
LOS	Length of stay

LTF	Lost to Follow-Up
mITT	Modified Intention-to-treat
mm	Millimeter
MRI	Magnetic Resonance Imaging
N	Sample Size
NL	Netherlands
OTC	Over the Counter
P4HB	poly-4-hydroxybutyrate
PE	Physical Examination
PP	Per Protocol
QoL	Quality of Life
RCT	Randomized Controlled Trial
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIP	Superficial Incisional Secondary
SIS	Superficial Incisional Primary
SOC	Standard of Care
SSI	Surgical Site Infection
SSO	Surgical Site Occurrence
™	Trademark
unsched.	unscheduled
US	United States
VAC	Vacuum Assisted Closure system
VAS	Visual Analogue Scale
VHWG	Ventral Hernia Working Group

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1. INTRODUCTION

1.1. Background

The incidence of incisional hernias is 10 to 20 %, making it one of the most common surgical complications after laparotomy. [1, 3]

Ventral and incisional hernias are treated with surgery to relieve symptoms (pain and discomfort), to prevent complications (strangulation, respiratory dysfunction, or skin problems), or to resolve acute complications (incarceration, perforation and strangulation).

There are several options for repair, including primary repair, synthetic or biologic material placement, repair with relaxing incisions, component separation and use of musculofascial flaps, utilizing both open and laparoscopic approaches. [5, 6, 7] However, there is no clear-cut consensus regarding the optimal hernia repair technique, particularly in complex hernia repair cases where patient co-morbidities exist and a high risk of infection is present.

Primary suture repair has been associated with a high risk of hernia recurrence, with reports ranging from 10% to 55%, and has been nearly abandoned for the repair of hernias which are greater than five centimeters (cm) in size. [3, 4, 5] As a result, most ventral hernia repair procedures involve the use of a mesh.

Synthetic mesh repair procedures, either open or laparoscopic, have been reported to lead to fewer recurrences compared to primary repairs.[2, 3, 4, 6] Improved outcomes are believed to be related to reduced tension on the fascial edges and sutures when mesh is used in hernia repair procedures. However, complex cases and large abdominal wall defects continue to pose a challenge to surgeons. Factors such as patient co-morbidities, defect size, location, tissue viability and degree of contamination are included in a surgeon's assessment and decision-making process.[10] These large abdominal wall defects have been associated with recurrence rates of up to 46%.[10]

Despite reducing hernia recurrence rates, the use of synthetic mesh has been associated with complications such as infection, pain, adhesions, fistulae, and foreign body reactions including increased inflammation and/or connective tissue deposition.[11]

Non-resorbable meshes can lead to complications related to the body's reaction to the persistent foreign mesh material resulting in foreign body sensations including discomfort and chronic pain, which is described by the International Association for the Study of Pain as pain lasting for 3 months or greater following hernia repair.[12, 13]

Ideally, a resorbable mesh should provide adequate structural support throughout the healing process and at the same time it should be fully resorbed when the wound has completely healed, thereby potentially reducing the chances for complications associated with the persistence of non-resorbable mesh material. However, the development of resorbable mesh products has faced challenges related to the rate of absorption with complications arising when the mesh product is resorbed too quickly. Rapid resorption does not support sufficient healing if structural reinforcement is diminished during the tissue repair period. A resorbable mesh should retain its functional strength for a

sufficient period of time to allow native cellular ingrowth tissue remodeling, maturation of collagen, and gradual shift of mechanical load.

Phasix™ Mesh is a commercially available medical device. It is a resorbable mesh prepared from poly-4-hydroxybutrate (P4HB) which has been studied for use as a biomaterial for a number of applications in medical devices and tissue engineering due to favorable mechanical properties, biocompatibility and desirable degradation times.[14, 15, 16] Using standard measures of mechanical strength (suture pull-out, tear and ball burst strength) Phasix™ Mesh is comparable in performance to traditional polypropylene mesh. Per the Instructions for Use (IFU), pre-clinical implantation studies indicate that Phasix™ Mesh retains approximately 70% of its strength at 12 weeks. Absorption of the mesh material will be essentially complete in 12-18 months. Given the long-term strength retention observed in preclinical studies, it is anticipated that Phasix™ Mesh may result in low recurrence and complication rates with minimal pain and discomfort when used for hernia repair.

A Prospective, Multi-Center Study of Phasix™ Mesh for Ventral or Incisional Hernia Repair of 121 subjects is ongoing in the United States. All subjects will be at 12 months follow-up in January 2016. Inclusion criteria include: 1. Primary ventral, incisional or recurrent (not to exceed 3) incisional hernias undergoing retro-rectus or onlay repair, 2. Presence of 1 or more comorbid conditions (obesity, smoking, diabetes mellitus, chronic steroid use, COPD, coronary artery disease, immunosuppression, hypoalbuminemia, renal insufficiency, age>75), 3. Hernia size > 10 cm^2 and < 350 cm^2, 4. CDC Class 1 wound. Demographic information, operative details, quality of life surveys, visual analog pain scores and postoperative outcomes are measured at 1, 3, 6, 12, 18, 24 and 36 months. As per June 2015 there have been two recurrences and no unexpected adverse events. The adverse events have not occurred with a greater frequency or severity than expected.

A Prospective, Multi-Center All Comers Study of a Novel Resorbable Mesh (Phasix™ Mesh) for Ventral or Incisional Hernia Repair is an ongoing single-arm interventional study of 25 subjects to collect additional data on safety, performance, and effectiveness of Phasix™ Mesh in subjects requiring primary ventral or incisional hernia repair out to 24 months follow-up.

This post-commercialization clinical study is being conducted to evaluate the use of Phasix™ Mesh in incisional midline hernia repair in Ventral Hernia Working Group (VHWG) Grade 3 patients. All treated subjects will be followed for 24 months post-implantation.

1.2. Rationale

This study is intended to evaluate the use of Phasix™ Mesh in VHWG Grade 3 patients in terms of performance and safety. Until now the use of Phasix™ Mesh was studied primarily in patients up to VHWG Grade 2, i.e. broad data on its use in a population of higher risk will be gained from this study. From a general perspective, the current literature still is rather void of evidence-based guidelines regarding optimal choice of mesh. Biologic meshes are mostly used in these cases, since mesh infection is anticipated postoperatively.

Hence, based on the data gained from this clinical study additional evidence may be provided with a view to optimal selection of hernia repair material. Another aspect of this clinical study deals with the investigation of cost-effectiveness concerning the use of Phasix™ Mesh in VHWG Grade 3 patients. The most wide-spread treatment option in patients with potentially infected surgeries currently consists in the use of cost-intensive biologic repair materials.

The combination of the features of the Phasix™ Mesh as proven in previous clinical and non-clinical investigations (resorbable with constant repair strength, monofilament structure) and based on evidence from this clinical study, Phasix™ Mesh may become a treatment alternative in VHWG Grade 3 patients.

1.3. Device Descriptions

The Phasix™ Mesh (manufacturer: Davol Inc.) is a resorbable mesh prepared from poly-4-hydroxybutyrate (P4HB). P4HB is produced from a naturally occurring monomer and is processed into monofilament fibers and knitted into a surgical mesh. Phasix™ Mesh degrades through a process of hydrolysis and a hydrolytic enzymatic digestive process. It was developed to minimize the variability of resorption rate (loss of mass) and strength and provide support throughout the expected period of healing.

Pre-clinical implantation studies indicate that Phasix™ Mesh retains approximately 70% of its strength at 12 weeks. Absorption of the mesh material will be essentially complete in 12-18 months.

Phasix™ Mesh has been commercially available in the US since 2012 and received CE Marking in 2015. As per its EEA approved intended use Phasix™ Mesh is indicated to reinforce soft tissue where weakness exists in patients undergoing abdominal plastic and reconstructive surgery, or for use in procedures involving soft tissue repair of ventral or inguinal hernias, or other abdominal fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result. Since Phasix™ Mesh is fully resorbable, it should not be used in repairs where permanent wound or organ support from the mesh is required. A full description of Phasix™ Mesh is included in the product's IFU.

2. STUDY OBJECTIVES

The objective of this study is to collect additional data on safety and performance of Phasix™ Mesh in subjects requiring VHWG Grade 3 midline hernia repair. The study end points are described below.

3. STUDY ENDPOINTS

3.1. Primary Endpoint

Surgical Site Occurrence (SSO) rate up to and including, the 3-month (± 14 days) follow-up assessment.

Occurrences at the surgical site will be assessed by physical examination at each study visit through 3 months (± 14 days). Surgical site occurrence will be defined as hematoma, seroma, surgical site infection, wound dehiscence, skin necrosis and fistula requiring intervention.

3.2. Secondary Endpoints

1. Surgical Site Occurrence (SSO) rate > 3-month follow-up assessment
2. Hernia Recurrence Rate (via physical exam, if uncertain via ultrasonography, if uncertain, via CT/MRI)
3. Surgical Site Infection rate (see 18.1)
4. Pain - Visual Analog Scale (VAS)
5. Device related adverse event incidence
6. Rate of reoperation due to the index hernia repair
7. Quality of life assessments (Carolinas Comfort Scale® and EQ-5D™)
8. Surgical procedure time as measured from incision to closure (skin to skin)
9. Return to work
10. Length of hospital stay (day of index surgery until day of discharge, LOS)

4. STUDY DESIGN

Approximately 85 subjects, at approximately 12 sites will be enrolled and treated to study the use of Phasix™ Mesh. All treated subjects will be followed for 2 years post-implantation. Follow-up visits will be conducted at Drain Removal per standard of care (SOC), 1, 3, 6, 12, 18 and 24 months following implantation. See Section 6 for a detailed schedule of study visits and procedures.

From the date of Phasix™ Mesh implant to each subject's 3 month assessment visit, the following safety reassessment applies:

Greater than 4 device-related SAEs or greater than 1 device-related recurrence.

If the criteria for reassessment are met:

1. Enrollment and implantations are suspended until the impact of the study parameters (e.g., surgical technique, hernia size/mesh size, protocol deviations (if any), AE time-course) on the results is assessed by the safety committee.
2. The follow-up for the subjects already treated continues.

5. STUDY POPULATION

5.1. Number of Subjects

This study is projected to treat 85 subjects with Phasix™ Mesh at approximately 12 sites. For the calculation of the sample size see section 7.1.

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

The subject must meet all of the criteria listed below to be enrolled in the study:

1. Subject must be 18 years of age or older.
2. Subject must be diagnosed with incisional midline hernia.
3. Subject has a VHWG Grade 3 hernia (as defined in 5.2.3).
4. Size of hernia ≥ 10 cm^2.
5. Subject must be willing to undergo a planned retro-rectus hernia repair (onlay allowed as an exception when retro-rectus placement cannot be achieved; using absorbable suture) with or without Component Separation Technique (CST).
6. The subject is legally competent, has been informed of the nature, the scope and the relevance of the study, voluntarily agrees to participation and the study's provisions, and has duly signed the informed consent form (ICF). Subject agrees to comply with the protocol-mandated procedures and visits.

5.2.2. Exclusion Criteria

The subject must be excluded from study enrollment if any of the following criteria are met:

1. Subject with > 4 previous repairs of the hernia under observation.
2. Body Mass Index (BMI) > 35 kg/m^2.
3. The subject is on, or suspected to be placed on, chemotherapy medications during any part of the study.
4. The subject has peritonitis.
5. Known human immunodeficiency virus (HIV) infection (if documented in the subject's record).
6. The subject has cirrhosis of the liver and/or ascites.
7. Subject is American Society of Anesthesiology Class 4 or 5.
8. Complete removal of existing mesh from a prior hernia repair (in the same affected area) is not possible.
9. The hernia repair requires more than a single piece mesh (with adequate overlap beyond the margins of the defect on all sides).
10. Subject has intact permanent mesh adjacent to the current hernia to be repaired.
11. Subject's hernia repair requires intraabdominal mesh placement.
12. Surgical technique requires surgical bridge repair as the sole repair.
13. Subject has any condition that, in the opinion of the Investigator, would preclude the use of the study device, or preclude the subject from completing the follow-up requirements.
14. Subject is pregnant or has plans to become pregnant during the study period or is currently breastfeeding.
15. Subject has an alcohol/substance abuse problem or has had a relapse within 12 months of the screening visit.
16. Subject was involved in another interventional clinical study in the last 30 days prior to ICF signature.
17. Subject is part of the site personnel directly involved with this study.
18. Subject has a life expectancy of less than 2 years at the time of enrollment.

19. Subject has a known sensitivity to Phasix™ Mesh or component materials (patients with known allergies to tetracycline hydrochloride or kanamycin sulfate should be avoided).

5.2.3. Definition of VHWG Grade 3 Hernia for this protocol

The table below provides some examples of surgical cases that would be considered Grade 3 or Grade 4. This is not a complete or definitive list.

Grade 3 Included	**Excluded** (considered Grade 4)
Previous wound infection after previous laparotomy	Active infection
Small bowel resection with anastomosis	Infected Mesh
Take down of ileostomy (or colostomy) with ileocolonic anastamosis	Uncontrolled spillage into surgical site
Creation of a stoma	Active fistula
Violation of the GI tract	Surgical site contains pus
Stoma present	Abscess
Cholecystectomy during hernia repair	

The table below provides examples of commonly planned concomitant procedures and how they would affect the hernia grading assessment.

Other Concomitant Procedures	**Grade Determination**
Repair of small bowel serosal tears	Grade 2
Hysterectomy	Grade 2
Bilaterial salpingo-oophrectomy	Grade 2
Repair of epigastric hernia	Grade 2
Bladder repair	Grade 3
Superficial cautery injury to loop of bowel with no deserosalization	Grade 2 (if no enterotomy)
Jejunostomy	Grade 3
Gastrectomy	Grade 3

6. STUDY PROCEDURES

6.1. Subject Screening and Baseline Evaluation

Subjects with a diagnosis of incisional midline hernia requiring surgical repair to close the defect who are presenting at the study site will be considered potential subjects for inclusion in this clinical study and should be pre-screened for study eligibility. If inclusion criteria are potentially met and no exclusion criteria are anticipated to be present at the time of such pre-screening (except for the informed consent which still needs to be

obtained), the Investigator will discuss the study and invite the patient to participate in accordance with the processes as described in section 14.3.3 in order to seek their informed consent to be given. Within 60 days from having obtained the subjects' informed consent, they will be screened for potential eligibility against the study protocol inclusion and exclusion criteria, utilizing ordinary standard of care procedures (e.g. physical examination, blood work, medical evaluation).

Written informed consent must be obtained prior to performance of any protocol specific procedures.

The following screening/baseline procedures will be conducted and documented.

6.1.1. Informed Consent

The investigator will explain the study to the subject, answer all of the subject's questions, and obtain written informed consent in a language in which the subject is fluent before the collection of any study data or performance of any study procedures.

The subject must have signed and dated the informed consent form prior to the collection of study data or performance of any study procedures. Documentation of the Informed Consent process must be present in the medical record and/or source documents. The original, signed informed consent will be retained with the subjects' records and a copy provided to the subject.

6.1.2. Enrollment

Subjects who sign an informed consent will be considered enrolled in this study. Subjects who provide consent for participation but do not meet all of the study eligibility criteria and do not receive the study device will be considered screen failures.

6.1.3. Eligibility

The subject's eligibility for study enrollment will be reviewed and documented in the appropriate eCRF. At the time of screening, a related progress note must be entered in the source documentation to indicate that all eligibility criteria were reviewed and screening results noted. Final eligibility will be determined intraoperatively.

Subjects who fail to meet eligibility criteria should be considered screen failures and treated according to the Investigator's standard of care. Data are to be collected for screen failure subjects from the time the ICF is signed until the subject is deemed a failure. At a minimum, subject demographics and the reason for failure must be collected; adverse events (AEs) will also be collected and followed through satisfactory resolution or stabilization.

6.1.4. Assignment of Subject Screening Number

Subject numbers will be assigned in sequential order, consisting of eight digits where the first two letters designate the country, the next three digits designate the study site and the last three digits designate the subject number (i.e., subject number NL 101 001 will be the

first subject at site 101 in the Netherlands; NL 101 002 will be the second subject at site 101, etc.).

6.1.5. Demographics and Medical History

The subject's medical history and demographic information will be documented in medical records and on the appropriate eCRF. Demographic information will include sex, age, race and ethnicity (as appropriate in the respective countries).

6.1.6. Physical Examination

A standard physical examination, appropriate to subjects about to undergo abdominal surgery, will be performed by the physician. Height and weight measurements will be recorded to allow for the calculation of BMI.

Length and width of the hernia should be described, as well as surgical site assessment (signs of infection, status and location of potential previous mesh, signs of necrosis).

6.1.7. Concomitant Pain Medication Usage

All current prescription and over the counter (OTC) pain medication must be recorded in the source documentation and in the eCRF on the pain medication log page at baseline. In addition, all pain medication related to AEs must be recorded during the course of the study.

6.1.8. Patient Reported Outcome Assessments

Subjects will complete the Pain VAS, Carolinas Comfort Scale® and EQ-5D™ to measure pain, discomfort and quality of life.

6.2. Surgical Procedure

All subjects will undergo an open ventral repair of hernias. The size of the hernia is an intraoperative inclusion criterion and must be greater than 10 cm^2. All other intraoperative exclusion criteria should be verified (e.g., absence of an active infection; presence of peritonitis; requirement of a hernia bridge as the sole repair procedure). Defect closure must be confirmed.

The surgical technique will require retro-rectus (onlay is allowed as an exception when retro-rectus placement cannot be achieved), using resorbable suture, with or without Component Separation Technique (CST). Subjects will be administered antibiotics according to hospital protocol. Subjects will be prepared to undergo hernia repair with Phasix™ Mesh following the instructions supplied by the manufacturer.

Phasix™ Mesh will be placed in the retro-rectus space with resorbable sutures. The peritoneum should remain posterior to the mesh upon completion of mesh placement. Mesh may be cut to shape or size desired for each specific application. To prevent recurrence when repairing hernias, a mesh larger than the defect is required to ensure

adequate coverage. The mesh is to be positioned so its edges extend beyond the margins of the defect by at least 5 cm. It is recommended that fixation be placed at approximately 5 to 6 cm intervals (6 to 12 resorbable sutures) around the periphery of the mesh. The edges are then fixated to assure proper closure under correct tension.

The procedure may include CST to obtain site closure. All incisions will be closed with staples and/or sutures and wounds will be dressed with sterile occlusive dressings.

The following information will be collected in the eCRF:

- Intra-operative evaluation of wound and abdomen
- Intra operative assessment and description of hernia
- Intraoperative assessment of complications e.g. enterotomy
- Surgical procedure
- Mesh details
- Fixation details
- Pre- and post-operative wound assessment
    - Signs of infection
    - Status and location of potential previous mesh
    - Signs of necrosis
- Wound closure
- Adverse Events
- Device failure/ malfunction/ defects

6.3. Subject Follow-up

6.3.1. Subjects not Implanted and Surgical Repair Failures

Subjects who are screened but do not meet the inclusion criteria or who fulfill one or more of the exclusion criteria shall be considered a screen failure and will be treated per hospital standard of care.

Reason for failure of the surgical repair procedure, as well as all information outlined in the Day of Surgery eCRFs must be recorded in the source documentation.

6.3.2. Subjects Successfully Implanted

Subjects successfully implanted with Phasix™ Mesh will be followed as per the protocol defined follow-up procedures (see Table of Study Events).

6.3.3. Subjects Completed the Study

Subjects who completed the study (regular or premature termination) will be subject to the common medical standard for further treatment of their condition.

6.3.4. Assessments

Subjects should report to the study site for visits at the following times post-implantation:

- Drain removal: per site's SOC
- 1 month: Day 30 ± 7 days
- 3 months: Day 90 ± 14 days
- 6 months: Day 180 ± 30 days
- 12 months: Day 365 ± 60 days
- 18 months: Day 545 ± 60 days
- 24 months: Day 730 ± 60 days

At each study visit (also unscheduled/early termination visits), the following procedures will be completed and these data recorded in source documentation and on the eCRF:

- Physical examination to check for hernia recurrence and surgical complications. Note: If the subject undergoes imaging for any reason and a recurrent hernia is identified, it must be recorded.
- Surgical Pain Scale (VAS, about the last 24h)
- Carolinas Comfort Scale® (except at Drain Removal visit)
- EQ-5D™ (except at Drain Removal visit)
- Assessment of AEs/complications
    - Pain related medication should be documented in the pain medication log page
    - Concomitant medication at the time of SAE and medication to treat the SAE will be documented on the SAE page
- Device failure/ malfunctions/ defects

In addition the following will be documented and recorded:

- At month 12 and month 24 the current hernia associated pain medication usage

6.3.5. Unscheduled Visits

The investigator can choose to see the subject more frequently if needed or required; however, these visits will not be recorded as study visits unless they are directly related to study procedures (Adverse Events, etc.).

6.4. TABLE OF STUDY EVENTS

Study Procedure	Screening and Baseline	Index Surgery	Drain Removal[4]	1 Month Visit	3 Month Visit	6 Month Visit	12 Month Visit	18 Month Visit	24 Month Visit	Unsched Visit / Early Term
Visit Window (days)	**Within 60 days of ICF signed**	**0**	**Per SOC**	**30 ± 7**	**90 ± 14**	**180 ± 30**	**365 ± 60**	**545 ± 60**	**730 ± 60**	**--**
Describe study to potential subject	**X**									
Obtain informed consent	**X**									
Collect demographics and medical history	**X**									
Verify eligibility criteria	**X**	**X[1]**								
Physical examination	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Placement of Device		**X**								
Pain Scale (VAS)	**X**		**X[2]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Carolinas Comfort Scale®	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**
EQ-5D™	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Collect adverse events		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Collect pain medications[3]	**X**						**X**		**X**	
Schedule follow-up visit	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		

[1] Intraoperative verification of inclusion/ exclusion criteria
[2] Assessment **BEFORE** Drain Removal
[3] AE related pain medication should be documented on the pain medication log page
[4] In the case no drains were placed, the assessments will be done at day of discharge. In case several drains are placed and pulled at different time points, assessments on any of the days of drain removal is allowed.

6.5. Withdrawal and/or Early Termination

Following treatment, every subject should remain in the study until completion of the required follow-up period; however a subject's participation may be discontinued. Should this occur, the reason for discontinuation must be captured in the source documentation. Potential reasons for discontinuation may include, but are not limited to the following:

- Subject Withdrawal: Subject participation in a clinical study is voluntary, and the subject may discontinue participation (refuse all subsequent testing/follow-up) at any time without penalty or loss of benefits. Subjects who withdraw will not be replaced.
- Investigator Termination: The Investigator may terminate the subject's participation without regard to the subject's consent if the Investigator believes it is medically necessary. Subjects terminated by the Investigator will not be replaced.
- Lost-to-Follow-up: The subject does not complete a scheduled follow-up but has not "officially" withdrawn from the study. (This does not apply to missed visits, where the subject misses one or more of the follow-up contact time points, but completes a subsequent one). In order to consider a subject lost-to-follow-up, site personnel should make all reasonable efforts to locate and communicate with the subject. A minimum of 3 attempts to contact the subject should be recorded in source documentation, including date and name of site personnel trying to make contact. Subjects who are lost to follow up will not be replaced.
- Other

A subject is considered an Early Termination (ET), if discontinuation occurs after study treatment and before 24 months follow-up. The site should attempt to bring the subject back to complete all ET visit study procedures (see Table of Study Events) prior to ultimately declaring the subject's discontinuation. In particular, in case a subject is willing to withdraw consent, the investigator should seek without exerting any pressure to the patient the subject's willingness to have an ET visit conducted prior to the formal declaration of withdrawal of consent.

Once a subject discontinues from the study, the Investigator must complete the End of Study page in the eCRF and the reason for subject discontinuation should be documented whenever possible.

7. STATISTICAL METHODS

This section describes the planned statistical analyses for this study. A detailed Statistical Analysis Plan (SAP) will be completed and placed on file prior to database lock. The SAP will contain a comprehensive explanation of the methodology used in the statistical analyses described below.

7.1. Sample Size Considerations

This is a feasibility study aiming to collect additional data on safety and performance of Phasix™ Mesh in subjects requiring VHWG Grade 3 midline hernia repair. There is no formal hypothesis test in this study and the result of the study is not for claiming purpose.

The study plans to include 85 subjects for follow-up, meaning 85 subjects having been treated with Phasix™ Mesh. Assuming an attrition rate of about 10%, 75 subjects will be evaluable to assess the primary endpoint of Surgical Site Occurrence (SSO) at 3 months. The expected rate of SSO at 3 months is 37% based on historically data. With 75 subjects, the accuracy of the estimated rate of SSO will be +/- 11% (i.e., half of the width of the 95% confidence interval of the estimated rate of SSO is 11%).

7.2. Data Analysis

During the study a continuous safety review will be done. In the case the criteria for safety assessment are met, a safety evaluation will be performed describing demographics, pre-operative and surgical diagnosis (incl. hernia assessment), surgical procedure, adverse event, SSO, hernia recurrence and protocol deviations (if any).

An interim analysis will be performed as soon as all subjects have documented the 3 month visit or have withdrawn from the study earlier. All data will be analyzed based on the modified intention-to-treat (mITT) population (definition see below) until the 3 month visit.
Unplanned interim analyses may also occur, for instance when all subjects have reached the 12 month follow-up visit.

The Intention-to-treat (ITT) population consists of all enrolled subjects. The mITT population is defined as those subjects in the ITT population in whom Phasix Mesh has been implanted.

A Per-Protocol (PP) population may be created if there are subjects who have any major protocol deviations. The PP population will consist of any subjects in the mITT population who do not have any major protocol deviation. The protocol deviations that are considered to have a “major” grade will be defined a priori in the SAP. All analyses will be primarily based on the mITT population. Primary analyses may be performed for PP population as well.

Demographics and baseline characteristics will be summarized using the mITT population. Summary statistics for categorical variables will include frequency counts and percentages and for continuous variables mean, standard deviation, minimum, median and maximum. Subjects’ demographics and eligibility criteria (including reason for failure in case of screen failure) will be listed for the ITT set.

The primary endpoint is the SSO rate up to (including) 3 months (± 14 days) post device placement based on the mITT population. A 95% confidence interval will be reported for the SSO rate.

The SSO rate after 3 months post device placement, the hernia recurrence rates until 1, 3, 6, 12, 18 and 24 months post device placement and surgical site infection rates until 1, 3, 6, 12, 18 and 24 months post device placement will be reported by visit along with their 95% confidence intervals based on the mITT population as secondary endpoints. Additionally, Kaplan-Meier analyses for the time from surgery to hernia recurrence and for the time from surgery to surgical site infection may be performed.

The secondary endpoints of VAS pain scale, Carolinas Comfort Scale® and EQ-5D™ will be summarized based on the mITT population with mean, standard deviation, minimum, median and maximum presented by visit. Device-related adverse events will tabulated by system organ class and preferred term (Medical dictionary for regulatory activities). The rate of subjects with a post procedure reoperation due to the index hernia repair will be presented by time intervals (until 1 month, 3 months, 6 months, 12 months, 18 months and until 24 months post device placement), Surgical procedure time of the index procedure (calculated as time of skin closure complete minus time of first incision) and length of hospital stay will be summarized descriptively. The time to return to work will be tabulated using summary statistics as well.
Safety parameters, such as adverse events, device deficiencies (mechanical failure, malfunction or defects), physical examination and pain medication, will be summarized using the mITT population.

Subgroup analyses will be performed by sex, sites (sites with few treated subjects can be combined) and other factors of interest.

No missing value imputation methods will be applied in any of the aforementioned analyses.

8. ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. All AEs that occur during the study should be treated with established standards of care that will protect the life and health of the study subjects.

AEs will be collected from the time of implantation (AE onset during or after index surgery) through the end of study participation (either study completion or early discontinuation) and will be documented in the medical record or source document and on eCRF. All events will be followed to satisfactory resolution or stabilization.
Events starting after ICF signature, but before implantation procedure will be documented as medical history in the medical record or source document and on eCRF.

8.1. Definition of Adverse Event

In this study, an AE is defined as any undesirable clinical event occurring in the abdominal space including the lower abdominal, inguinal and pubic regions (including the skin), as well as any other undesirable clinical events judged to be related to the study device or surgical procedure regardless of anatomical region. Additionally, abnormal laboratory results are to be considered AEs if the results are accompanied by clinical signs or symptoms. The Investigator will assess the relationship of an AE to the study device or procedure as described in Section 8.5.

8.2. Definition of Adverse Device Effect

An Adverse Device Effect (ADE) is an AE related to the use of the mesh product implanted. This includes AEs resulting from insufficient or inadequate IFU, deployment, implantation, installation, or operation, or any malfunction of the Phasix™ Mesh.

Additionally, this definition includes any event resulting from use error or from intentional misuse of the Phasix™ Mesh.

8.3. Definition of Serious Adverse Event

An event will be classified as a serious adverse event (SAE) if it meets the definition of serious in the ISO 14155:2011(E) as listed below:

An adverse event is considered serious if it:

a) led to a death,

b) led to a serious deterioration in health that:

1) resulted in a life-threatening illness or injury, or

2) resulted in a permanent impairment of a body structure or a 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.

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE 1: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

NOTE 2: For this study only Adverse Events according to the modified definition as per section 8.1 need to be collected in the eCRF. However, all Serious Adverse Events need to be reported, regardless of anatomical region or relatedness to surgical procedure or device.

8.4. Serious Adverse Device Effect

A Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of an SAE.

8.5. Relationship of Adverse Event to Device/Procedure

Assess each AE for its relationship to Phasix™ or surgical procedures as follows:

- Device: This category should be restricted to AEs directly attributable to the device used as part of the study procedure.

- Procedure: This category should be restricted to AEs directly attributable to the study device surgical procedure.

Use the following categories for assigning the certainty of the relatedness:

- Definitely Related: An AE is definitely related if it is obvious, certain or there is little doubt regarding the relationship.
- Possibly Related: An AE is possibly related if it is capable of being related but relatively unlikely.
- Not Related: An AE is not related if it is determined that there is no plausible association.

8.6. Severity of Adverse Events

Each AE should be assessed for its severity, or the intensity of an event, experienced by the subject.

- Mild: Awareness of a sign or symptom that does not interfere with the subject's activity or is transient and is resolved without treatment or sequelae.
- Moderate: May interfere with the subject's activity and require additional intervention and/or treatment, and may have additional sequelae.
- Severe: Significant discomfort to the subject and/or interferes with the subject's activity. Additional intervention and/or treatment are necessary. Additional sequelae occur.

8.7. Reporting of Adverse Events

If an AE occurs, all sections of the appropriate eCRF page must be completed.

All Investigator-judged device-related AEs that occur (whether serious or not) must be reported to Davol Inc. Field Assurance within 24 hours of becoming aware of the event.

Additionally, all SAEs (whether device- or procedure-related or not) must be reported to the Sponsor within 24 hours of becoming aware of the event.

The Sponsor will report to the Food and Drug Administration (FDA) and to National Competent Authorities in Europe and other involved parties as per ISO 14155:2011(E) after becoming aware of a reportable event, as applicable per the corresponding national regulations.

The provisions of Directive 93/42/EEC concerning information and notification of incidents occurring following placing devices on the market are fully applicable and remain with the investigator and manufacturer correspondingly.

9. SAFETY COMMITTEE

The Safety Committee will consist of three members. The members will be selected on the basis of relevant experience and understanding of clinical research and the issues specific to the therapeutic area, as well as previous Safety Committee experience. Membership will be completely independent of the investigation and will have no financial, scientific, or other conflict of interest with the study, including the product used in this study.

From the date of Phasix™ Mesh implant to each subject's 3 month assessment visit, the following safety reassessment applies:

If more than 4 device-related SAEs or more than 1 device-related recurrence occur(s):

1. Enrollment and implantations are suspended until the impact of the study parameters (e.g., surgical technique, hernia size/mesh size, protocol deviations (if any), AE time-course) on the results is assessed.
2. The follow-up for the subjects already treated continues.

If the criteria for safety reassessment are met, the safety committee will evaluate the safety of the study protocol and decide about potential adaptations to the protocol and/or further enrollment.

The further details of the Safety Committee will be documented in the Safety Committee Charter.

10. DEVICE DEFICIENCY REPORTING AND MANAGEMENT

All device deficiencies occurring during the conduct of this study will be reported by the Investigator to the Sponsor without unjustified delay. The further management of device deficiencies by the Investigator and the sponsor/manufacturer will adhere to the appropriate national laws and regulations.

11. ELECTRONIC CASE REPORT FORMS

The Investigator is responsible for ensuring the accuracy and completeness of all study documentation. All clinical study data will be recorded in the eCRF provided to the investigational site.

12. RISK/BENEFIT ANALYSIS

Subjects participating in this study will require hernia repair surgery as part of their standard of care. The device utilized in this study is commercially available, has 510(k) clearance from the US FDA, has a CE marking and will be used in accordance with the intended use as outlined in the IFU which is in place for the European market. This study will not pose any additional potential risk to the health, safety, or welfare of the subject. The only additional risks posed by this study are related to data collection and the privacy of the patient's personal health information. The risks associated with hernia repair and the mesh used in this clinical investigation are described in full in the corresponding IFU.

There is no immediate benefit to the subject for participation in this study. Collection and analysis of the data generated in this study may be of benefit to future subjects who require hernia repair.

13. DATA COLLECTION AND MONITORING

13.1. Data collection

The Investigator (or designated hospital staff) will assure primary data collection based on source-documented hospital chart reviews.

13.1.1. Electronic Case Report Form (eCRF)

All required clinical data for this trial will be collected in web-based standardized eCRFs. Site and subject numbers will be used to track subject information throughout the study. The eCRF is designed to accommodate the specific features of the study design. Modification of the eCRF will only be made if deemed necessary by Davol Inc. and/or the appropriate ethics committee (EC) and/or regulatory body.

13.1.2. Monitoring

Each site will have an initiation visit performed by a Study Monitor. This visit will ensure that the Investigator understands his/her responsibility for conducting this study at his/her center.
Sites will be monitored according to the approved monitoring plan. Monitoring personnel will monitor for accuracy and timely submission of data forms and compliance with the study protocol, meeting enrollment commitments, applicable regulations, the signed Investigator Agreement and any conditions of approval imposed by the reviewing EC and/or regulatory agencies.

The Study Monitors will maintain personal contact with the Investigator and staff throughout the study by phone, mail, and on-site visits. The Study Monitors will compile and submit to Davol Inc. a monitoring report after each visit that will include any findings, conclusions, and actions taken to correct deficiencies.

13.1.3. Source Documentation

Auditors, monitors, the study Sponsor and regulatory authorities may have access to the medical records related to this study. Original or certified copies of all relevant clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the medical file of each enrolled subject. No source documentation will be recorded directly on an eCRF. The Investigator will permit study–related monitoring, audits, EC review and authority inspections by allowing direct access to the source data.

In case of electronic source data, access will be allowed or dated print-outs will be available prior to the monitoring visits.

13.1.4. Data Management

Prior to enrollment of the first subject a Data Management Plan (DMP) will be developed outlining the procedures used for data review, database cleaning and issuing and resolving data queries. Procedures for validations and data storage will also be contained within the DMP.

13.1.5. Record Retention

The Sponsor and Investigator will maintain accurate, complete and current records relating to the conduct of the investigation according to national requirements. The data for some of these records may be available in computerized form from the CRO, but the final responsibility for maintaining study records remains with the Investigator.

The investigator shall retain all study records for a period of at least 2 years after the investigation is terminated or completed. The investigator may withdraw from the responsibility to maintain records for the period required and transfer custody of the records to any other person who will accept responsibility for retaining them with pre-approval. Notice of a transfer shall be given to the Sponsor not later than 10 working days after transfer occurs.

14. ADMINISTRATIVE REQUIREMENTS

This study will be conducted in accordance with ISO 14155:2011, the Declaration of Helsinki in its currently recognized version, and any national and local regulations.

14.1. Publication Policy

Davol Inc. acknowledges that relevant study outcomes, positive or negative, must be made available to interested parties, especially physicians and regulators. In addition, this study will be posted on ClinicalTrials.gov and the Basic Results will be reported there, in accordance with applicable law.

At the conclusion of the study, a multi-center article may be prepared for publication in a scientific journal. The publication of the principal results from any single-center experience is not allowed until the preparation and publication of the multi-center results as premature discussion of study data can give rise to real or perceived biases that can compromise the integrity of the study outcomes. As such, exceptions to this rule require the prior approval of Davol Inc.

For purposes of timely abstract presentation and publication, such publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multi-center data will require the approval of Davol Inc.

14.2. Investigator Selection

The Investigator must be of good standing as an Investigator and knowledgeable in relevant areas of clinical research and in the medical discipline investigated in this clinical study to ensure adherence to the requirements of the protocol, including the

protection of human subjects. Other site personnel must have appropriate research experience and infrastructure to ensure adherence to the protocol and enrollment of sufficient numbers of evaluable subjects. The curriculum vitae (CV) of the Investigator will be maintained in the Sponsor files as documentation of previous medical training, and federal databases will be searched to ensure that the Investigator and/or the site are not prohibited from engaging in federally Sponsored clinical research. The Principal Investigator will sign the signature page of this protocol, agreeing to comply with all applicable government regulations and the requirements of this study.

14.3. Regulatory and Ethical Considerations

14.3.1. Ethics Committee Approval

Investigators or designees must submit the study protocol together with all locally required documentation to their EC and obtain written favorable opinion before being allowed to participate in and conduct the study. Annual re-approval must also be obtained, if applicable per local regulation. The Investigator or designee is also responsible for fulfilling any conditions of approval imposed by the EC, such as regular safety reporting, study timing, etc. The Investigator or designee will provide Davol Inc. with copies of such approvals and reports.

Any amendments to the protocol, as well as possible associated information and consent form changes, will be submitted to the EC and written favorable opinion obtained prior to implementation, as required per national laws and regulations.

14.3.2. Authorization from / notification to competent authority

National competent authorities will be sought authorization from or will be notified on the conduct of this study in accordance with the requirements of the applicable national laws and regulations.

Any amendments to the protocol, as well as possible associated information and consent form changes, will be notified to, or approved by the national competent authorities, if required.

14.3.3. Informed Consent

Prior to the procedure, the Investigator (or designee) must explain to each subject in layman's terms, the nature of the study, its purpose, expected duration, and the benefits and risks of study participation. Also, subjects will be informed of uses and disclosures of their medical information for research purposes and their rights to access information about them. The subjects must be informed of their rights to withdraw from the study at any time for any reason without sanction, penalty, or loss of benefits to which they are otherwise entitled, and that withdrawal from the study will not jeopardize their future medical care. After this explanation and before entering the study, the subject must voluntarily sign and date the EC-approved ICF. The subject will receive a copy of their ICF.

If, during the course of the study, new information becomes available that might affect the subjects' or otherwise take influence on the subjects' continued willingness of

participation in this clinical study, they will be informed thereof in accordance with the procedures described above for obtaining their informed consent. Subjects should be re-consented in such a situation.

14.3.4. Confidentiality

All information and data sent to Davol Inc. or an authorized designee concerning subjects or their participation in the study will be considered confidential. All data used in the analysis and reporting of this study will be used in a manner without identifiable reference to the subject. The Investigator consents to visits by personnel of Davol Inc. and its affiliates or designees, as well as, FDA representatives.

14.4. Protocol Adherence, Deviations and Amendments

A protocol deviation is defined as an event where the clinical Investigator or site personnel did not conduct the study according to the Investigational Plan.
It is the Investigator's responsibility to ensure that there are no deviations from the investigational plan except where necessary to protect the life or physical well-being of a subject in an emergency. Continued protocol deviations may result in termination of enrollment in the study at the site.

Deviations must be reported within the eCRF regardless of whether medically justifiable or taken to protect the subject in an emergency. Investigators will also adhere to procedures for reporting study deviations to their EC in accordance with their specific EC reporting policies and procedures.

14.5. Device Accountability

Only commercially available surgical mesh products will be used. Device accountability will not be required.

14.6. Subject Compensation

Subjects will be reimbursed at a fixed rate to cover their travel costs to the clinic for each on-site follow-up visit that they complete.

15. TERMINATION OF STUDY

Sponsor reserves the right to suspend enrollment or terminate the study at any time as set forth in the Clinical Study Agreement. Written notice will be submitted to the Investigator in advance of such termination.

Sponsor may suspend enrollment or terminate the study at a specific site for reasons including, but not limited to, inadequate data collection, low subject enrollment rate, achievement of the total enrollment, or non-compliance with the protocol or other clinical research requirements.

16. STATEMENT OF COMPLIANCE

This clinical investigation will be conducted in compliance with the clinical investigation plan (CIP) and the following regulatory requirements:

• International Standard ISO 14155:2011: Clinical investigation of medical devices for human subjects - Good clinical practice (GCP)
• Declaration of Helsinki adopted by the 18thWorld Medical Assembly in Helsinki, Finland, in 1964, in its currently recognized revision
• Applicable sections of the national laws and regulations.

By acting in accordance with this CIP, the Sponsor, the Investigators and the study site personnel fulfill the requirements of the International Standard ISO 14155:2011.

The clinical investigation will not commence at a clinical site until favorable opinion(s) from the respective ethics committee(s) (ECs) have been received. All additional requirements imposed by the EC(s) will be followed. Involvement of the national competent authorities, e.g. by notification, seeking authorization, will be accomplished as required by national laws and regulations.

Insurance coverage for damages emerging from the clinical investigation will be provided according to applicable legal requirements.

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18. APPENDIX

18.1. Appendix A: Surgical Site Infection Criteria[17]

Superficial Incisional Surgical Site Infections (SSI)
Infection occurs within 30 days after the operative procedure (where day 1 = procedure day)
AND
involves only the skin or subcutaneous tissue of the incision
AND
at least ***one*** of the following:

A. Purulent drainage from the superficial incision or subcutaneous tissue.
B. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
C. Superficial incision that is deliberately opened by a surgeon, attending physician or other designee and is culture positive or not cultured
   AND
   Patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat. A culture negative finding does not meet this criterion.
D. Diagnosis of a superficial incisional SSI by the surgeon or attending physician or other designee.

COMMENT: There are two specific types of superficial incisional SSIs:

1. Superficial Incisional Primary (SIP) –a superficial incisional SSI that is identified in the primary incision in a patient that has had an operation with one or more incisions (e.g., C -section incision or chest incision for CBGB)
2. Superficial Incisional Secondary (SIS) – a superficial incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than one incision (e.g., donor site incision for CBGB)

The following do not qualify as criteria for meeting the definition of superficial SSI:

- Diagnosis/treatment of cellulitis (redness/warmth/swelling), by itself, does not meet criterion d for superficial incisional SSI. An incision that is draining or culture (+) is not considered a cellulitis.
- A stitch abscess alone (minimal inflammation and discharge confined to the points of suture penetration).

- **Deep Incisional SSI**

Infection occurs within 90 days after the operative procedure (for herniorrhaphy) (where day 1 = procedure day)
AND
involves deep soft tissues of the incision (e.g., fascia and muscle layers)
AND
patient has at least ***one*** of the following:

a. Purulent drainage from the deep incision.
b. A deep incision spontaneously dehisces or is deliberately opened or aspirated by a surgeon, attending physician or other designee and is culture positive or not cultured
   AND

patient has at least ***one*** of the following signs or symptoms: fever (>38°C), localized pain or tenderness. A culture negative finding does not meet this criterion.

c. An abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test.

COMMENTS: There are two specific types of deep incisional SSIs:

1. Deep Incisional Primary (DIP) –a deep incisional SSI that is identified in a primary incision in a patient that has had an operation with one or more incisions (e.g., C-section incision or chest incision for CBGB)
2. Deep Incisional Secondary (DIS) – a deep incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than one incision (e.g., donor site incision for CBGB)

- **Organ/Space SSI**

Must meet the following criteria:
Infection occurs within 90 days after the operative procedure (for herniorrhaphy)(where day 1 = procedure day)

AND

infection involves any part of the body deeper than the fascial/muscle layers, that is opened or manipulated during the operative procedure

AND

patient has at least ***one*** of the following:

a. purulent drainage from a drain that is placed into the organ/space (e.g., closed suction drainage system, open drain, T-tube drain, CT guided drainage)
b. organisms isolated from an aseptically-obtained culture of fluid or tissue in the organ/space
c. an abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test

AND

meets at least ***one*** of the organ/space infection site "intraabdominal" criteria:

1. Patient has organisms cultured from abscess and/or purulent material from intraabdominal space.
2. Patient has abscess or other evidence of intraabdominal infection on gross anatomic or histopathologic exam.
3. Patient has at least two of the following signs or symptoms: fever (>38.0°C$^{\pm}$), nausea*, vomiting*, abdominal pain*, or jaundice*

AND

at least one of the following:

a. organisms seen on culture or Gram stain of drainage or tissue obtained during invasive procedure or from an aseptically-placed drain (e.g., closed suction drainage system, open drain, T-tube drain, CT guided drainage)
b. organisms cultured from blood and imaging test evidence suggestive of infection (e.g., ultrasound, CT scan, MRI, radiolabel scans [gallium, technetium, etc.] or on abdominal x-ray), which if equivocal is supported by clinical correlation.

* With no other recognized cause
± As documented in the medical record