STATISTICAL ANALYSIS PLAN

Title: A Prospective, Multi-Center All Comers Study of a Novel Resorbable Mesh (Phasix™ Mesh) for Ventral or Incisional Hernia Repair

Protocol No.: DVL-HE-015

Study Device: Phasix™ Mesh

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1 Introduction

This document provides details of the statistical analysis plan (SAP) for the C.R. Bard, Inc. protocol DVL-HE-015 for the final analysis. The statistical methods described here are based on the analyses proposed in the Final Protocol issued on **August 21, 2014, Version 3.0.**

All data processing, summarization, and analyses will be performed using Statistical Analysis System (SAS), Version 9.3 software package.

2 Study Objective and Endpoints

2.1 Study Objective

The objective of this single-arm observational study is to collect additional data on safety, performance, and effectiveness of Phasix™ Mesh in subjects requiring primary ventral or incisional hernia repair.

2.2 Study Endpoints

2.2.1 Primary Endpoint

Hernia Recurrence Rate

Hernia recurrence rates will be assessed by physical examination at each study visit through 24 months. A recurrent hernia will be defined as any hernia identified or confirmed by the investigator, during any study follow-up visit, in approximately the same position as the hernia repaired in the study procedure. Potential hernias identified via incidental magnetic resonance imaging (MRI) or computed tomography (CT) scan will be evaluated by the operating surgeon for clinical significance and confirmation of hernia recurrence.

2.2.2 Secondary Endpoints

1. Device related adverse event incidence
2. Quality of life assessments (Carolinas Comfort Scale® and SF-12® - 12-item short form health survey)
3. Surgical procedure time as measured from incision to closure (skin to skin)
4. Length of hospital stay post index surgical procedure
5. Number of study-related post-operative surgical procedures and admissions
6. Number of study-related post-operative visits unrelated to standard of care.
7. Incidence of Seroma.

3 Study Design

3.1 Overview

This is a prospective, multi-center, single-arm, observational study designed to collect additional data on safety, performance and effectiveness of Phasix™ Mesh for primary ventral or incisional or first-recurrent hernia repair. Follow-up visits will be conducted at 1, 3, 6, 12, 18, and 24 months following surgery. See Section 3.3, Table 1 for a detailed schedule of study visits and procedures.

3.2 Sample Size Consideration

This study is projected to enroll up to 30 subjects at approximately 5 sites. The sample size of 30 subjects is based on potential adequacy of data to meet the study objectives. It is not based on any statistical consideration.

3.3 Study Procedure

An overview of the study visit schedules is shown in Table 1, which summarizes the study procedures to be performed at each study visit.

Table 1: Time and Events Schedule

Study Procedure	Screening and Baseline Period	Surgery	1 Month Visit	3 Month Visit	6 Month Visit	12 Month Visit	18 Month Visit	24 Month Visit	Unscheduled Visit/Early Termination
Visit Window (days)	**Within 60 days of consent**	**0**	**30 ± 7**	**90 ± 30**	**180 ± 30**	**365 ± 30**	**545 ± 30**	**730 ± 30**	**--**
Describe study to potential subject	**X**								
Obtain informed consent	**X**								
Verify eligibility criteria	**X**	**X**							
Collect demographics and medical history	**X**								
Conduct physical examination	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Placement Procedure of Device		**X**[1]							
Carolinas Comfort Scale®	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
SF-12®	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Collect adverse events/ complications		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Collect pain medication usage	**X**					**X**		**X**	

[1] See Protocol Section 6.2 for surgical procedure details

4 Analysis Sets

The Intent-to-treat (ITT) population consists of all enrolled subjects who have signed the Informed Consent Form. The modified ITT (mITT) population is defined as those subjects in the ITT population in whom Phasix™ Mesh has been implanted. All analyses will be primarily based on the mITT population.

4.1 By visit interval

There are several tables needed by interval presentation. If the data are collected at each assessment, then the interval will be targeted at each of the visit. If the data are collected by date only on unscheduled CRF, it will be used to separate the intervals. See below table as guidance on how to separate the intervals.

		Interval	
Visit	Visit Window	Term	Days
1 month	Day 30 ± 7 days	Post OP – 1 month	0-37 days
3 month	Day 90 ± 30 days	>1 month – 3 month	38-120 days
6 month	Day 180 ± 30 days	>3 month – 6 month	121-210 days
12 month	Day 365 ± 30 days	>6 month – 12 month	211-395 days
18 month	Day 545 ± 30 days	>12 month – 18 month	396-575 days
24 month	Day 730 ± 30 days	>18 month – 24 month	576 days-end of study/760 days (whichever is earlier)
End of Study (if > 24 month upper window)	NA	>24 months - End of Study	761 days-end of study

5 Statistical Analysis of the Primary Endpoint

There is no formal statistical hypothesis for this observational post-market study. The study will follow eligible patients implanted with the Phasix™ Mesh for hernia repair in order to assess long-term recurrence rates.

The primary endpoint of the study is Hernia Recurrence Rate.

Hernia recurrence will be assessed by physical examination at each study visit through end of study. A recurrent hernia will be defined as any hernia identified or confirmed by the investigator, during any study follow-up visit, in approximately the same position as the hernia repaired in the study procedure. Potential hernias identified via incidental magnetic resonance imaging (MRI) or computed tomography (CT) scan will be evaluated by the operating surgeon for clinical significance and confirmation of hernia recurrence.

The event will be identified if either of the following questions on "HERNIA RECURRENCE" was answered "Yes":

> "Was there any Evidence of Hernia Recurrence in the Same Approximate Location as the Index Procedure Identified by Physical Exam?"

or

> "Was there any Evidence of Hernia Recurrence in the Same Approximate Location as the Index Procedure Identified by Any Other Means?"

Only the first hernia recurrence of each subject will be counted in the calculation of the hernia recurrence rate. The hernia recurrence rate will be reported for the whole follow up period (post-op to end of study) and by visit using the intervals defined in section 4.1. Only the subjects who did not discontinue the study before the visit window start will be included in the denominator. The 95% confidence intervals of the rates will be estimated by the Binomial exact method.

Kaplan-Meier survival analysis will be performed to estimate the event rates at various time-points (1 month, 3 month, 6 months, 12 months, 18 month, 24 month, End of Study (if out of 24 month visit upper window)). The time to first event will be the time from index-procedure to the first occurrence of the first event.

6 Statistical Analysis of the Secondary Endpoint

The following secondary endpoints will be summarized using descriptive statistics. The secondary endpoints are described in Section 2.2.2.

6.1 Device related adverse event incidence

Adverse events that are possibly or definitely related to device are considered. A frequency table grouped by Medical Dictionary for Regulatory Activities (MedDRA dictionary version 16.1) terms (system organ class (SOC) and preferred term (PT)) will be presented.

A frequency table for device related AEs for the whole follow up period (post-op to end of study) and by time intervals (post OP – 1 month/ > 1 month – 3 months/ > 3 months – 6 months/ > 6 months – 12 months/ > 12 months – 18 months/ > 18 months – 24 months/ > 24 months (if any)) presenting the number of events and number of subjects with events will be displayed.

6.2 Quality of life assessments (Carolinas Comfort Scale® and SF-12® - 12-item short form health survey)

The CCS is a 23-item questionnaire that measures three scales: sensation of mesh, severity of pain and movement limitations in the following eight domains: laying down, bending over, sitting up, performing activities of daily living, coughing or deep breathing, walking, walking up the stairs and exercising. The CCS is completed by the subjects at baseline and at all post procedure visits. Each scale score (range from 0-5) is the average across the domains, and the total score (range from 0-5) is the average of the three scales scores.

The CCS three scales scores and total score and their absolute changes from baseline will be descriptively tabulated by visit.

Note: At baseline the scale score “sensation of mesh” and the total score will be calculated for subjects with recurrent hernia and used mesh (see pre-operative diagnoses), if enough values are available. In case of sufficient entries for sensation of mesh at baseline, the absolute change from baseline will be calculated for the scale score “sensation of mesh” and the total score in the subset of subjects with recurrent hernia and used mesh.

The SF-12 version 2 is a multipurpose, 12-item health survey that measures seven domains of health: general health, physical functioning, role limitations due to physical health (role-physical), role limitations due to emotional problems (role-emotional), bodily pain, vitality and mental health, social functioning. It yields scale scores for each of these seven health domains, and two summary measures of physical and mental health: the physical component summary (PCS) and mental component summary (MCS). The SF-12 is completed by the subjects at baseline and at all post procedure visits.

The SF-12 domains and summary measures and their absolute change from baseline will be descriptively tabulated by visit, if scores are available.

6.3 Surgical procedure time as measured from incision to closure (skin to skin)

The surgical procedure time (mins) of the index procedure is calculated as time of skin closure complete minus time of first incision. Summary statistics will be presented for surgical procedure time.

6.4 Length of hospital stay post index surgical procedure

The length of hospital stay (days) is calculated as date of hospital discharge (documented at index procedure) minus date of hospital admission (documented at surgery day (day 0)). The length of hospital stay will be descriptively tabulated.

6.5 Number of study-related post-operative surgical procedures and admissions

Study-related post-operative surgical procedures and admissions will be identified by the AE data with study related AE and requires either "Necessitates Medical or Surgical Intervention" or "New Hospital Admission" (or both). Study related AEs include Possibly Related or Definitely Related to the Device or Procedure. The number of study-related post-operative surgical procedures and admissions for each subject will be summarized for the whole follow up period (post-op to end of study) and by time intervals (post OP – 1 month/ > 1 month – 3 months/ > 3 months – 6 months/ > 6 months – 12 months/ > 12 months – 18 months/ > 18 months – 24 months/ > 24 months (if any)).

6.6 Number of study-related post-operative visits unrelated to standard of care

All unscheduled visits with "Non-Standard of Care" checked will be considered study related post-operative visits unrelated to standard of care. The number of study-related post-operative visits unrelated to standard of care of each subject will be presented for the whole follow up period (post-op to end of study) and by time intervals (post OP – 1 month/ > 1 month – 3 months/ > 3 months – 6 months/ > 6 months – 12 months/ > 12 months – 18 months/ > 18 months – 24 months/ > 24 months (if any)).

6.7 Incidence of Seroma

Seroma will be identified from AE. A frequency table for seroma for the whole follow up period (post-op to end of study) and by time intervals (post OP – 1 month/ > 1 month – 3 months/ > 3 months – 6 months/ > 6 months – 12 months/ > 12 months – 18 months/ > 18 months – 24 months/ > 24 months (if any)) will be presented.

7 Statistical Analyses of Other Endpoints

7.1 Subjects Dispositions

The summary of the number of subjects enrolled (intent to treat (ITT)), treated with Phasix™ Mesh (mITT), completed the study, and discontinued from the study (by reason of discontinuation) will be provided. Screen failures will be summarized for inclusion/exclusion criteria that were not met.

7.2 Protocol Deviations

The number of subjects with protocol deviations will be summarized with descriptive statistics by nature of the deviation. Protocol deviations will be listed with date of occurrence and the nature of deviation.

7.3 Demography and Background Disease Characteristics

Demographics and background disease characteristics will be summarized with descriptive statistics using the mITT analysis set. Summary statistics for categorical variables will include frequency counts and percentages and for continuous variables will include mean, standard deviation, minimum, median, and maximum.

Demographics and baseline characteristics variables include:

- Age at screening (year)
- Sex (Male, Female)
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino)
- Baseline Weight
- Baseline Height
- Baseline Body Mass Index (BMI) calculated from weight and height.

Weight change over time and BMI change over time will be summarized by visit.

Background disease characteristics including medical history (in 5 categories: cardiac disease, respiratory illness, renal disease, vascular disease and other; and in sub-terms) and hernia assessment will be summarized.

7.4 Prior/concomitant medication

All current pain medication is captured at baseline. Hernia associated pain medication is captured at 12 and 24 months.

A frequency table by Baseline, Month 12 and Month 24 visit will be presented showing the intake of prescription or OTC medications including the classification in “non-narcotic” and “narcotic”.

7.5 Follow-up Period

The duration of follow-up period after the surgery during the study is calculated as:

Last day in study – date of the surgery.

Last day in study is defined as latest of: discontinuation/completion day, last visit day, last event occurrence day.

The hospital duration after the surgery during the study is calculated as:

Date of the discharge – date of the surgery.

7.6 Intra-operative characteristics

The procedural overview and surgical details data will be summarized by subject with descriptive statistics; the drain data will be summarized by drain.

7.7 Device failure, malfunctions and defects

The investigator records if the surgical mesh device used in the study procedure failed to meet its performance specifications whether due to mechanical failure, malfunction or defects. Device failures, malfunctions or defects will be tabulated by the failure code.

7.8 Safety Endpoints

7.8.1 Adverse Event

Adverse events will be collected from the time of enrollment through the end of study participation (either study completion or early discontinuation) and will be documented on the medical record or source document and on study eCRFs. Events with an onset prior to enrollment should be reported in the subject's medical history. AEs will be coded using MedDRA version 16.1. AEs will be summarized by system organ class and preferred term.

The number and percentage of subjects with at least one AE, total number of AEs, AEs by relationship to the device/procedure, AEs by severity of the event, and serious AE will be summarized.

Listing of all AEs, as well as all SAEs will be provided.

7.8.2 Mesh Infection

A frequency table for Mesh Infection for the whole follow up period (post-op to end of study) and by time intervals (post OP – 1 month/ > 1 month – 3 months/ > 3 months – 6 months/ > 6 months – 12 months/ > 12 months – 18 months/ > 18 months – 24 months/ > 24 months (if any)) presenting the number of events and number of subjects with events will be displayed.

7.8.3 Surgical Site Infection

Surgical site infection is collected per Center for Disease Control and Prevention (CDC) ("Guideline for Prevention of Surgical Site Infection, 1999").

A frequency table for Surgical Site Infection for the whole follow up period (post-op to end of study) and by time intervals (post OP – 1 month/ > 1 month – 3 months/ > 3 months – 6 months/ > 6 months – 12 months/ > 12 months – 18 months/ > 18 months – 24 months/ > 24 months (if any)) presenting the number of events and number of subjects with events will be displayed.

7.8.4 CDC Wound Classification

Wound Classification is collected per Center for Disease Control and Prevention (CDC) ("Guideline for Prevention of Surgical Site Infection, 1999").

Wound Classification will be summarized at baseline, pre-operative and post-operative and shift from previous visit will be presented.

7.8.5 Reoperation

The re-operation will be summarized by subject and by reoperation with descriptive statistics; the drain data will be summarized by drains, if applicable.