STATISTICAL ANALYSIS PLAN

Title: A Post-Market, Prospective, Multicenter, Single-Arm Trial of XenMatrix™ AB Surgical Graft in All CDC Wound Class Ventral or Incisional Midline Hernias

Protocol No.: DVL-HE-012

Study Type: Post-Market

Study Device: Bard® XenMatrix™ AB Surgical Graft

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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-012. An interim analysis of some or all study endpoints will be performed after all active subjects have a 45-days post device implantation. However, interim analyses may be performed at other time periods (e.g., 6-months) to assess the results. The statistical methods described here are based on the analyses proposed in the Final Protocol issued on **February 14, 2017, Version 2.0.**

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 study is to collect data on the performance and use of XenMatrix™ AB Surgical Graft for up to 24-months in subjects with ventral or incisional midline hernias, across all CDC wound classes in the retro-rectus or intraperitoneal location. The study end points are described below.

2.2 Study Endpoints

2.2.1 Primary Endpoint

The Primary endpoint is the proportion of subjects with Wound Occurrences in the first 45 days post-implantation. Wound Occurrences will be defined as surgical site infection, seroma, wound dehiscence, skin necrosis and fistulas requiring intervention.

2.2.2 Secondary Endpoints

1. Wound Occurrences > 45-days post-implantation
2. Rate of hernia recurrence
3. Rate of reoperation due to the index hernia repair
4. Quality of life assessments (Carolinas Comfort Scale® and SF-12v2®)
5. Return to work
6. Length of stay

2.3 Overview

This is a prospective, multicenter, single-arm clinical study to collect data on the performance and use of XenMatrix™ AB Surgical Graft for ventral or incisional midline hernia repair across patients in all CDC wound classes utilizing retro-rectus or intraperitoneal placement of mesh. The study will be conducted at approximately 10 U.S. sites to treat approximately 75 subjects. Follow-up visits will be conducted at 1, 3, 6, 12, 18, and 24-months following surgery.

3 Population 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 whom underwent placement of a XenMatrix™ AB Surgical Graft. Subjects who are enrolled but not treated with XenMatrix™ AB will be replaced to ensure 75 subjects are treated with the study device.

Per Protocol (PP) population will include all subjects in the mITT population except those who enter the study without meeting the inclusion/exclusion criteria.
All analyses will be primarily based on the mITT population.

4 Primary Endpoints

The primary endpoint is wound occurrence rate within the first 45 days post implantation.

4.1 Definitions

The primary endpoint of wound occurrence rate will be assessed within the first 45 days post-implantation. The following wound occurrences that require interventions will constitute the primary endpoint: surgical site infection, seroma, wound dehiscence, skin necrosis and fistulas. The above events recorded in the reoperation eCRF page, or in the AE eCRF page with "Intervention required"=Yes will be counted towards the primary endpoint. The start date of the event as recorded in the AE dataset will be considered the start date of the event.

4.2 Statistical Hypothesis

There is no formal statistical hypothesis for this study. The study will follow eligible patients across all CDC wound classes who undergo ventral or incisional midline hernia repair with the XenMatrix™ AB Surgical Graft in order to assess wound occurrences for 24-months period.

4.3 Primary Analysis

The proportions of subjects with wound occurrence up to 45-days, and 95% confidence intervals of the rate from exact binomial test, will be reported. Primary analysis is based on mITT population.

Reported start date (recorded in the AE data set) of the wound occurrence minus the date of the index hernia repair (implantation of the XenMatrix AB) will be used to determine if a wound occurrence occurred within 45 days from index surgery. Any subject discontinued before 45 days and does not have a wound occurrence that required intervention are considered as not evaluable and will be excluded from the analysis.

4.4 Sensitivity Analysis and Handling of Missing Data

The primary analysis will be performed without imputation for the missing data. As secondary analysis, the rates of the primary endpoint will be estimated using the Kaplan-Meier method along with 95% confidence interval. Number of subjects with events, number of subjects censored and number of subjects left will also be presented.

The time to first event will be the time from index-procedure to the occurrence of the first event (as recorded in the AE data set). Subjects who do not have a wound occurrence requiring intervention before 45 days and do not discontinue the study before day 45 will be censored at day 45; subjects who discontinue before day 45 will be censored by their discontinuation day. If subjects discontinue at the surgery day then day 0.5 will be used as censor date. Note, the circumstances may be described separately.

A Kaplan-Meier graph will also be provided showing the survival curves for female and males separately on the same page.

4.5 Data Pooling

Data from all investigational sites will be pooled for analysis. Sites will be tested for potential differences in the primary endpoint. Sites with fewer than 10 treated subjects will be combined for this purpose. If there is significant variation among sites, the rates of the primary endpoint and associated 95% confidence interval will be estimated using a logistic regression with sites included in the model as a random effect.

5 Evaluation of Secondary Endpoints

5.1 Wound Occurrence > 45-days post-implantation

The proportion of subjects with wound occurrence >45 days post-implantation (including all events that occurred post day 45 and are available at the time of the report) and confidence intervals of the rate from exact binomial test will be reported.

If a subject discontinued within (≤) 45 days after index surgery, that subject is considered not evaluable and will be excluded from calculation of wound occurrence rate after 45 days follow-up.

Analysis is based on mITT population.

5.2 Rate of Reoperation due to Index Hernia Repair

The proportion of subjects with reoperation due to the index hernia repair (as recorded in the reoperation eCRF page) and confidence intervals of the rate from exact binomial method will be reported by visit, including both cumulative and disjoint intervals.

Reoperation date will be compared to surgery date to determine the interval of reoperation.

Only evaluable subjects will be included in the denominator and evaluable subjects are defined as following: 1) For cumulative intervals, any subjects with XenMatrix™ AB implanted will be included in this analysis. 2) For disjoint intervals, if a subject discontinues before the intervals begins then that subject is considered as not evaluable for that particular interval analysis. Analysis is based on mITT population.

5.3 Quality of life assessments (Carolinas Comfort Scale® and SF-12v2®)

5.3.1 Carolinas Comfort Scale (CCS)

The CCS is a 23-item questionnaire that measures 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 (sensation of mesh, pain or movement limitations) score (ranges from 0-5) is the average across the domains, and the total score (ranges from 0-5) is the average of the three scales scores.

CCS will be analyzed in accordance to the CCS user guide. Computational algorithms including the handling of missing values are described in detail in the guideline. In summary, the following rules will be applied:

1. Questions outcomes 0-5 will be used with lower scores indicating a more favorable health status.
2. Not applicable or no response will be handled as missing values.
3. Two or more outcomes ticked per question will be handled as missing value.

Absolute values and changes from baseline will be summarized with mean, standard deviation, minimum, median and maximum for each scale score and total score at each post baseline visit (except drain removal).

For each subject at each visit, if less or equal to two responses are missing within any of the three scales, the missing values will be replaced by the mean of the remaining responses of the scale at that visit. If more than two responses are missing within any scale for a visit, the whole survey at that visit will not be used for that subject.

Analysis is based on mITT population.

5.3.2 SF-12v2®

The 12-items in the SF-12v2® are subset of those in the SF-36®. The SF-12v2® includes one or two items from each of the eight health concepts. Thus, the SF-12v2® measures eight concepts: Physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health.

The eight health concepts will be summarized in two components: Physical Components Summary, and Mental Component Summary. Data will be analyzed based on the guidelines of the SF-12v2® instrument.

Analysis is based on mITT population.

5.4 Return to Work

The return to work (days) of the index procedure is calculated as the date of return to work minus the date of the index hernia repair.

Descriptive Summary statistics will be presented for return to work. Analysis is based on mITT population.

5.5 Length of Stay in Hospital (Day of Index Surgery until Day of Discharge, LOS)

The LOS (days) at index procedure is calculated as date of hospital discharge (index procedure) minus date of hospital admission).

Descriptive Summary statistics will be presented for length of stay. Analysis is based on mITT population.

6 Subgroup Analysis

By sex subgroup analysis will be performed for primary and Kaplan-Meier analysis (tables and curves) for primary and some secondary endpoints.

Where appropriate, further subgroup analysis (based on the mITT set) may be performed for the primary endpoint if enough subjects within the subgroups allow further insight to the data. Following subgroups are subject to further interest:

- Centers: The sites with less than 10 subjects will be sorted by site number within each country and pooled by order to form one or more combined site(s) with at least 10 subjects. The pooling will be restricted within country.
- Surgical Technique: 'Retro-rectus with CST', 'Retro-rectus without CST', 'Intra-Abdominal with CST', 'Intra-Abdominal without CST' and 'Other'.
- Wound Classifications (CDC)
- Type of Midline Hernia (Ventral vs. Incisional)
- Type of Midline Herina (Primary vs. Recurrent)

7 Other Analysis

7.1 Subject Disposition

The summary of the number of subjects enrolled (ITT), implanted with XenMatrix™ AB (mITT), completed the study, and discontinued from the study by reason of discontinuation will be provided. Screen failures will be listed with inclusion/exclusion criteria that were not met. Summary may also be presented by site.

7.2 Protocol Deviation

The number of subjects with protocol deviations will be summarized by nature of the deviation. Protocol deviations will be summarized by site and period of occurrence. Additionally, protocol deviations will be listed with date of occurrence and the nature of deviation. Subjects who had the study device implanted while failing to meet the inclusion/exclusion criteria will be considered major protocol deviations, and will be excluded from the per protocol population.

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 (in years)
- Sex (Male, Female)
- Race (Asian, Black or African American, Caucasian and Other)
- Baseline Weight
- Baseline Height
- Baseline Body mass index (BMI) calculated from weight and height.
- Work status (employment status)

Background disease characteristics including medical history, wound classification, and hernia assessment will be summarized.

7.4 Pain Medication

All current pain medication is captured at baseline and all post implantation visits. Summary of the pain medication type will be provided.

7.5 Follow-up Period

The duration of follow-up period after the index surgery 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 or, last event occurrence day.

7.6 Surgical Details

Descriptive summaries of the surgical details will be provided.

7.7 Surgical Drains

Surgical drain data will be summarized by the number of drains, number of subjects with surgical drains, corresponding surgery, placement, location and duration.

7.8 Device Failures

Device deficiencies will be summarized with number of deficiencies, number of subjects with device deficiencies, deficiency codes and reasons.

7.9 Adverse Events

AEs will be collected from the time of enrollment (AE onset after signing ICF) through the end of study participation (either study completion or screen failure or early discontinuation) and will

be documented in the medical record or source document and on study eCRFs. All events will be followed to satisfactory resolution or stabilization. AEs that occur prior to the surgical procedure will be added to the medical history. AEs that occur from the time of surgical procedure will be recorded in the source documentation and on the AE page of the eCRF

AEs will be tabulated by system organ class (SOC) and preferred term (PT) (MedDRA 16.1). The total number of events, as well as the number and percentage of subjects with events will be reported. Subjects will also be summarized by severity groups. SAEs will be summarized by SOC and PT.

Subjects with AEs related to the procedure (definitely or possibly related; in case of a missing classification of the relationship to procedure a relation to the procedure is assumed) will be summarized with frequency and percentage. Device related AEs will be summarized similarly. Subjects who do not have XenMatrix™ AB implanted will have their AEs summarized separately and their outcome data will not be collected or analyzed.

8 Sample Size Considerations

This study is projected to enroll up to 75 subjects at approximately 10 sites in order to have 64 evaluable subjects at 24 months. It is anticipated that there will be a 15% loss to follow-up rate. The sample size of 64 evaluable subjects is based on potential adequacy of data to meet the study objectives. It is not based on any statistical consideration.