



An Acelyty Company

ABBREVIATED STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER

AHS.2012.Customizable.01

PRODUCT/PROJECT:

Prevena™ Customizable™ Dressing
Prevena Plus™ Customizable™ Dressing

TITLE:

The Management of Closed Surgical Incisions resulting from Incisional Hernia Repair and/or Functional Panniculectomy using the Prevena™ Customizable™ Dressing

PREPARED: September 15, 2017
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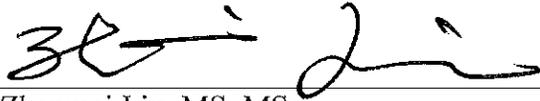
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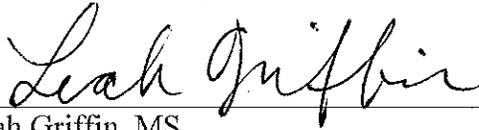


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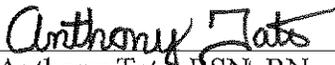
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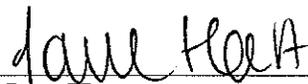
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LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
CI	Confidence Interval
CRF	Case Report Form
CRI	Clinically Relevant Interventions
Customizable™	Prevena™ / Prevena Plus™ Customizable™ dressing with ActiV.A.C
DOS	Day of Surgery
FAS	Full Analysis Set Population
ITT	Intent-To-Treat Population
MedDRA	Medical Dictionary for Regulatory Activities
POD	Post Operative Day
SAP	Statistical Analysis Plan
SOC	Standard of Care
SOP	Standard Operating Procedure
SP	Safety Population
SSC	Surgical Site Complications
SSI	Surgical Site Infection
TEAE	Treatment-Emergent Adverse Event

1. PURPOSE

The purpose of this abbreviated statistical analysis plan (SAP) for the AHS.2012.Customizable.01 study is to outline the analyses planned to support the completion of the Clinical Study Report (CSR) based on the requirements and guidelines identified by the U.S. Food and Drug Administration (FDA). This document is a supplement to the clinical protocol, which should be referred to for details regarding the study objective, design and endpoints.

2. OVERVIEW OF STUDY DESIGN

This is a post-market, open-label, prospective, randomized controlled study to evaluate the safety and effectiveness of Customizable™ when used to manage extensive vertical, transverse, and fleur-de-lis surgical incisions resulting from the primary closure of incisional hernia repair and/or functional panniculectomy procedures. Study data are analyzed for clinical outcomes through 34 days.

At the time of the interim data review, approximately 60 subjects will have been enrolled at two clinical sites in North America. Each subject will be randomized in a 1:1 ratio, stratified by clinical site and type of incision (fleur-de-lis vs. transverse/vertical), to receive either Prevena™ Customizable™ dressing/Prevena Plus™ Customizable™ dressing with ActiV.A.C (Customizable™) or Standard of Care (SOC). Subjects assigned to treatment with Customizable™ will receive treatment for five to seven days post surgery prior to removal of the treatment. Subjects in the SOC arm will receive treatment with standard of care surgical incision dressing one to three days prior to the removal of the treatment. Subjects will be assessed for surgical site complications (SSC) and clinically relevant interventions (CRI) at treatment removal and at Day 10, Day 14, Day 21 and Day 30 post-surgery visits. Subjects will also be assessed for any SSC and any CRI at any unscheduled visit.

The following table provides a general depiction of the study visit/period schedule.

Study Visit/Period	Study Day		
Screening Visit	0 - 45 days prior to surgery		
Surgery/ Randomization/ Treatment Application	Panniculectomy or Incisional Hernia Repair followed by randomization to Prevena™ Customizable™ dressing/Prevena Plus™ Customizable™ dressing with ActiV.A.C (Customizable™) or Standard of Care dressing (SOC).		
Treatment Period	<table border="1"> <tr> <td><u>Customizable™</u> 5-7 Days</td> <td><u>SOC</u> 1-3 days</td> </tr> </table>	<u>Customizable™</u> 5-7 Days	<u>SOC</u> 1-3 days
<u>Customizable™</u> 5-7 Days	<u>SOC</u> 1-3 days		
Follow-up Period	Follow-up visits at Days 10, 14, 21, and 30 and unscheduled visits.		

3. STUDY OBJECTIVE

The primary objective of the study is to compare surgical incision-related clinical outcomes in subjects undergoing abdominal surgery for incisional hernia repair and/or functional panniculectomy when managed with Customizable™ as compared to standard of care surgical incision dressing (dry sterile dressing/gauze, steri-strips).

4. EVALUATION CRITERIA

4.1 Primary Endpoint

The primary endpoint for this study is the subject incidence of surgical site complication (SSC) with Customizable™ as compared to the SOC treatment group. SSC is defined as one of the following:

- Dehiscence
- Surgical site infection (SSI)
 - Superficial SSI
 - Deep SSI

4.2 Secondary Endpoint

The secondary endpoint for this study is the subject incidence of clinically relevant interventions (CRI) of the surgical incision in Subjects managed with Customizable™ as compared to the control group managed with a SOC surgical incision dressing. For this study, clinically relevant interventions are defined as the following:

- Antimicrobial treatment of SSI
- Percutaneous and open drainage of the surgical incision (by surgeon)
- Debridement of the surgical incision
- Re-operation related to the surgical incision
- NPWT applied to the open surgical incision

No analysis for the secondary endpoint will be performed due to the early termination of the study.

4.3 Safety Endpoint

The safety endpoint for this study is adverse event (AE). All AEs will be captured at each study visit during treatment and follow-up visits regardless of causality or severity.

Defined in the study protocol, an AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including clinically significant abnormal laboratory findings) in subjects, whether or not related to the study product. This definition includes adverse event(s):

- Related to the study product or the comparator,
- Related to the study procedures involved,
- Resulting from user error or from intentional misuse of the study product.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1 Scope of Abbreviated Analysis

All analyses described in this abbreviated SAP will be based on the available data for all enrolled subjects. The scope of analyses will include:

- General Analysis: Enrollment, disposition, informed consent, baseline demographics and characteristics.
- Analysis for primary endpoint – Primary effectiveness analysis.
- Analysis of safety measures.

5.2 Sample Size and Power

Per the protocol, at the time of the trial design,

“A 35% rate of SSC is projected for the SOC arm, which is consistent with the clinical experience of the Investigators. Based on the primary endpoint of incidence rate of SSC, Fisher’s exact test with a two-sided significance level $\alpha = 0.05$ will have approximately 80% power to detect the difference between an incidence rate of 35% in the SOC arm and an incidence rate of 8.75% in the Customizable arm (a 75% reduction) when the sample size in each arm is 44. To account for possible Subject replacement, the sample will be increased by up to 15% for a maximum total of 102 Subjects (51 in each treatment arm).”

The study was terminated early before it reached the final planned sample size of 102 subjects. The study enrollment was stopped on Friday, June 30, 2017. The decision of early termination was made after the interim data review described in Section 10 of this document. A total of 71 subjects (36 in Customizable™, 35 in SOC) were enrolled in this study.

5.3 Analysis Populations

The following subject populations for this clinical study are:

Safety Population – The Safety population will consist of all subjects who are randomized and do not withdraw before the attempt to apply the assigned treatment with Customizable™ or SOC surgical incision dressing regardless of its duration. Subject data will be analyzed in the arm to which they were treated. All safety results for this study will be presented based on the safety population.

Intent-to-Treat (ITT) Population – The ITT population will consist of all subjects who are randomized and do not withdraw before the attempt to apply the assigned treatment with Customizable™ or SOC surgical incision dressing regardless of its duration. Subject data will be analyzed in the arm to which they were randomized. All supportive or exploratory analyses for this study will be presented based on the ITT population.

Full Analysis Population (FAS): The FAS subject population will consist of all subjects who i) met all of the pre-operative and intra-operative inclusion criteria and none of the pre-operative and intra-operative exclusion criteria, ii) have been randomized, and iii) received treatment with either Customizable™ or SOC dressing. Subjects without SSC will need to receive at least 5 days of Customizable™ or at least 1 day of SOC dressing to be included in this set and completed Day 30 (\pm 4 days). Subjects with SSC prior to Day 30 (\pm 4 days) will be included in this set regardless of length of Customizable™ or SOC dressing treatment and treatment follow up. Subject data will be analyzed in the arm to which they were randomized and treated. The primary and secondary effectiveness analyses for this study will be based on the FAS population.

Subjects having important disqualifying protocol deviations will be excluded from ITT and/or FAS based on the results from the protocol deviation review described in Section 5.4 of this document.

5.4 Conventions, Definitions and Handling of Missing Data/Dropouts

5.4.1 General Considerations

- Summaries of continuous variables will show the number of non-missing values (n), along with mean, median, standard deviation, minimum and maximum. In general, the maximum and minimum values will be presented to the same precision as the raw data; the mean and median will be presented to one decimal place more than the raw data. The standard deviation and confidence intervals (CI) will be presented to two decimal places more than the raw data. Exceptions for number of decimal places may be made according to the data. The p-values will be presented to four decimal places. A p-value less than 0.0001 will be presented as < 0.0001 or $< .0001$.
- Listings of all available data recorded on the case report form (CRFs) will be presented. There will be no imputation of missing data, with the exception of partially missing dates.
 - Each analysis variable with partial dates will be reviewed at the time of analysis and final decision will be made at that point on the appropriate imputation strategy. All

subject listings data will be provided as recorded on the CRFs indicating the partial dates and missing data. If needed, footnote(s) for imputed dates will be added to the data listings.

- If data are missing or incomplete and the variable is used in a calculation then the derived variable will be set to missing. Similarly in the summary tables of analyses the variable will be considered missing.
- The most recent assessment prior to the Day 0 surgery or prior to the opening of the randomization envelope will be used as the baseline reference for all analyses which incorporate a baseline value.
- All end-of-study analyses will use the last recorded observation (last visit) during the study.
- All subjects enrolled in the study who received either Customizable™ or SOC will be included in the summary of safety profile.
- Protocol deviations will be defined as departures from the study protocol and could potentially affect clinical results or safety conclusions. All protocol deviations will be identified and recorded. Following applicable KCI standard operating procedures, the Protocol Deviation Review Committee evaluates the protocol deviation data and identifies all important disqualifying protocol deviations. The results from the review will be imported and incorporated in the corresponding analysis. A listing for all identified protocol deviations will be presented. Subjects disqualified from ITT or FAS analysis populations may be subsequently tabulated in summary tables.

5.4.2 Conventions/Imputations for Adverse Events

Any adverse event that started or worsened on/after the initial application of either Customizable™ or SOC will be analyzed as treatment-emergent.

If the adverse event (AE) start date has missing data (e.g., the year of the AE start date is missing, or the month of the AE start date is missing, or the day of the AE date is missing), then choose the missing components of the AE onset date and impute the AE onset date to be as close to being on/after the date of initial application of either Customizable™ or SOC as possible.

6. GENERAL STATISTICAL ANALYSES

Enrollment and subject disposition, informed consent, demographics and baseline disease characteristics will be summarized. Summary statistics will include n, mean, standard deviation, median, and range (minimum, maximum) for continuous variables, and frequencies and percentages for categorical variables.

6.1 Enrollment, Disposition

The number and percent of subjects randomized, treated, and assessed will be presented by treatment group in tabular form and a customized CONSORT diagram. The reasons for early withdrawal and discontinuation from the study will also be presented.

6.2 Demographics and Baseline Characteristics

The following subject data and characteristics will be presented by treatment group and overall:

- Clinical site
- Age , continuous
- Age by category
- Sex
- Race
- Ethnicity
- BMI kg/m²
- BMI by category
- Type of surgery
- Type of incision
- Panniculus grade
- Tranverse incision length
- Inverse incision length
- Panniculus weight
- Panniculus weight, category
- Risk factors (diabetes, immunosuppressent, current tobacco user, and vascular disease)
- Reported medical histories.

7. STATISTICAL ANALYSIS OF EFFECTIVENESS MEASURES

7.1 Primary Effectiveness Analysis

The primary endpoint will be analyzed on subjects in the Full Analysis Population. The incidence rate of SSC will be calculated for each treatment group as follows:

$$SSC\ rate = [Number\ of\ subjects\ who\ experienced\ an\ SSC] / [Full\ Analysis\ Population]$$

Subjects included in the numerator for the incidence computation must have experienced an SSC within 34 days after the initial study surgery. If a subject experiences one or more SSC events, the subject will be counted only once in the numerator. The number and percent of subjects experiencing each component of the SSC (dehiscence, superficial SSI, deep SSI, or any SSI) will also be presented.

The incidence rates of SSC results will be presented by treatment group and overall. The Fisher's Exact test with a 2-sided significant level $\alpha = 0.048$ will be used to compare the SSC incidence rates between two treatment groups. The null and alternative hypotheses are as the follows:

H₀: The Customizable™ and SOC treatment groups have equal incidence rates of SSC

$$SSC_{Customizable} = SSC_{SOC}$$

H₁: The Customizable™ and SOC treatment groups have different incidence rates of SSC

$$SSC_{Customizable} \neq SSC_{SOC}$$

If the incidence rate of SSC of Customizable™ is smaller than the incidence rate of SSC of SOC dressing (i.e. $SSC_{Customizable} < SSC_{SOC}$) and the P-value from the above Fisher's Exact test is below 0.048 (i.e. $P\text{-value} \leq 0.048$) then we conclude that the incidence rate of SSCs decreased statistically significantly in Customizable™ compared with SOC dressing in this clinical study.

As additional supportive analysis, the above analysis will be repeated based on the ITT population.

8. ANALYSIS OF SAFETY MEASURES

All subjects in the Safety Population will be evaluated for safety. Safety analyses will include summaries of adverse event rates. In general, the summary results of safety parameters will be based on descriptive statistics.

8.1 Adverse Events

All treatment emergent adverse events will be coded using MedDRA coding dictionary (Version 20.0) and analyzed. An adverse event will be considered as treatment emergent (TEAE) if the onset is any time on or after the initial study surgery, panniculectomy or incisional hernia repair, through any time post surgery.

Number and percentage of treated subjects experiencing any TEAE will be summarized by system organ class and preferred term. Summary tables will be provided of incidences for all treatment emergent adverse events, treatment-related adverse events, adverse events by maximum severity, serious adverse events, serious adverse events related to study product and adverse events that led to study discontinuation. In any given category (e.g., system organ class or preferred term) a subject will be counted only once. If a subject has the same adverse event on multiple occasions, only the one with maximum severity will be presented. The denominator for the calculation of percentages will be the number of subjects in the sub-arm of subjects being tabulated and not the number of events.

Listings providing all serious adverse events, discontinuations due to any adverse event, or deaths occurring during the course of the study will be presented by subject.

The following summary tables and listings will be presented by treatment group and overall:

- Incidence of all treatment emergent adverse events by system organ class and preferred term.
- Incidence of all serious treatment emergent adverse events by system organ class and preferred term.
- Incidence of treatment-related adverse events by system organ class and preferred term.
- Incidence of treatment-related serious adverse events by system organ class and preferred term.
- Incidence of all treatment emergent adverse events by system organ class, preferred term, and maximum severity.
- Listing of all serious treatment emergent adverse events.
- Listing of all treatment-related serious adverse events.
- Listing of discontinuations: Subjects who discontinued from study due to any treatment emergent adverse event.
- Listing of deaths: Subjects who died of any cause during study.

9. DESCRIPTION OF OTHER PLANNED ANALYSES

No other planned analyses will be performed.

10. INTERIM ANALYSES

As stated in the protocol,

“There is no formal planned interim analysis for this clinical study. However, there is one planned interim data review with one planned final data analysis. Planned interim data review will be conducted when approximately 60 subjects have completed Visit 9 or completed the study. Data from this interim data review will be used to verify the assumptions for sample size calculation or to re-estimate the sample size. The interim analysis will be based off of the ITT subject population of available data”

According to the study protocol and the interim data review plan, an interim data review was conducted on 61 subjects of the FAS from a total 70 treated subjects: 29 subjects in

Customizable™ and 32 subjects in SOC. The incidence rate of SSC of Customizable™ was 17.2% and the incidence rate of the SOC was 3.1%. Since the calculated SSC rates from the interim data review were outside of the ranges of the sample size assumptions used for the study design, an early termination of the study was recommended due to lack of evidence to support the objectives and assumptions of the study. All enrolled subjects including subjects enrolled before and after interim data review will be included in the final analysis according to this document. In the final analysis, the type I error rate ($\alpha=0.048$) for statistical significance may be used for the primary analysis using the O'Brien-Fleming method.

Both, the interim data review plan and the interim data review results, may be included in the final clinical study report for this study.

11. RANDOMIZATION RELEASE

As stated in the protocol,

“Subjects who meet all inclusion criteria and no exclusion criteria and who consent to participate in the study will be randomized in a 1:1 ratio to be treated with either Customizable or SOC surgical incision dressing. Due to the variances in complication rates between incision types, a stratified randomization will be used to ensure balance between the groups. The randomization will be stratified for each site and incision type of vertical/transverse and fleur-de-lis. Within each stratum, permuted blocks will be used to achieve equal numbers of Subjects assigned to Customizable or SOC surgical incision dressing. For each stratum, a randomization schedule will be generated to include Subject numbers and treatment assignments with the stratum of transverse/vertical incision starting with 1001 and the stratum of fleur-de-lis incision starting with 2001. Corresponding randomization envelopes will be prepared in sequential order by Subject number to provide randomization to each Investigator.

Randomization envelopes will be prepared corresponding to each row in the randomization schedule. Subject numbers will be printed and labeled clearly on the top of each envelope. Additionally, the envelopes will be color coded for incision type stratum, sealed, and organized by stratum and in ascending by Subject number.

Once the Subject has been screened, deemed eligible, and provided informed consent, the next available sequentially numbered randomization envelope within the corresponding stratum according to incision type; a sealed Customizable box and ActiV.A.C. unit will be taken into the operating room with the Subject. Randomization will be conducted in the operating room after closure of the surgical incision and confirmation of intra-operative eligibility. The envelope will be opened prior to surgical incision dressing placement and the assigned treatment arm will be

used. If Customizable is not selected, the sealed box and ActiV.A.C. unit will be returned to appropriate storage area.”

The randomization schedule for this study is a supplement to this statistical analysis plan and will be kept as a separate document.

Any deviation occurred during randomization process will be documented and corresponding actions/procedures will be followed. If a subject did not receive the assigned treatment by randomization, then the following actions will be performed:

1. Record the deviation in the protocol deviation file.
2. The subject will be analyzed according to actual treatment received in the Safety population.
3. The subject will be analyzed according to the randomized treatment in the ITT population.

12. QUALITY CONTROL/QUALITY ASSURANCE

Accurate, consistent, and reliable data will be ensured through the use of applicable KCI standard operating procedures, quality procedures, and work instructions.

All data listings, tables, and figures/graphs will be programmed using SAS Version 9.4 or later.