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| **Study Plan Title** | Hydromechanical Cleansing with V.A.C. VERAFLO CLEANSE CHOICE dressing and NPWTi-d vs. Collagenase Ointment in the Management of Full-thickness Wounds (ACCELERATE Trial) |
| **Study Number** | EM-05-015019 (formerly, KCI.CLEANSE.CHOICE.2017.01) |
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| **Biostatistician** | Shelley-Ann Walters |

## ELECTRONIC SIGNATURES:

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# 1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) for the EM# 05-014019 clinical investigation plan or CIP (formerly known as KCI.CLEANSE.CHOICE.2017.02) is to outline the analyses planned to support the generation and completion of the Clinical Study Report (CSR). This SAP has been written in accordance with the clinical protocol (Hydromechanical Cleansing With V.A.C. VERAFLO CLEANSE CHOICE™ Dressing and NPWTi-d vs. Collagenase Ointment in the Management of Full-thickness Wounds (Accelerate Trial), Version 5.0, 13 February 2020) and relevant data collection documents.

This SAP adheres to the requirements and guidelines identified by the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Post hoc exploratory analyses not defined in this SAP may be performed to further examine study data. Any post-hoc or unplanned exploratory analysis will be identified as such. This document will be endorsed prior to database lock. Changes made to the SAP before final database lock will be described in the document history. The SAP will not be amended after the final database lock. Deviations from planned analyses, including additional exploratory analyses after database lock, will be noted in the CSR.

# 2. STUDY OBJECTIVES

The primary objective of this study is to compare the short-term effects of the V.A.C.ULTA™ Negative Pressure Wound Therapy System with instillation therapy using normal saline and V.A.C. VERAFLO CLEANSE CHOICE™ Dressing to collagenase ointment in wounds (e.g., chronic, acute, traumatic, or dehisced wounds) and/or ulcers (full-thickness wounds).

# 3. INVESTIGATIONAL PLAN

## 3.1. Study Design

This study is a randomized, controlled, prospective multicenter study. After obtaining informed consent, undergoing screening procedures, and meeting all the inclusion criteria and none of the exclusion criteria listed in Protocol Section 4.2, qualified Subjects will receive either V.A.C. VERAFLO CLEANSE CHOICE™ Dressing and NPWTi-d (V.A.C. VERAFLO™ Therapy with saline solution) or collagenase ointment to manage their wound over 6-9 days following instructions in Protocol Section 3.1.1 and 3.1.2.

The study population will consist of Subjects diagnosed with full-thickness wounds (e.g., a chronic wound, an acute wound, a traumatic wound, wound dehiscence, and/or ulcers) that measure ≥ 16 $cm^2$ of total surface area, have a minimum width of 2 cm (excluding undermining) before sharp and/or mechanical removal of eschar at the bedside, and are < 20 cm across (edge-to-edge) at any point perpendicular to the wound edges.

Approximately 60 Subjects will participate in this study. The total duration of participation may include up to 10 days of screening and up to nine (9) days of treatment. Subjects may have up to an additional 30 days of follow-up for safety on treatment-related adverse events that have not resolved by the final follow-up visit on Day 6-9.

*The following devices and dressings will be applied for the two treatment groups:*

- *V.A.C.ULTA™ Negative Pressure Wound Therapy System with instillation therapy (i.e., V.A.C. VERAFLO™ Therapy) using V.A.C. VERAFLO CLEANSE CHOICE™ Dressing and normal saline*
- *Collagenase ointment with compatible standard dressing.*

## 3.2. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

**Table 1: Schedule of Events**

| Procedure Description | Visit 1<br>Screening<br>Day -10 to 0 | Visit 2<br>Random-ization<br>Day 0 | Visit 3[1]<br><br>Day 2-3 | Visit 4[1]<br><br>Day 4-6 | Visit 5[1]<br>End of Treatment<br>Day 6-9 | Un-scheduled |
|---|---|---|---|---|---|---|
| **Informed Consent** | X | | | | | |
| **Inclusion/Exclusion Criteria** | X | X[2] | | | | |
| **Demographics and Subject Characteristics** | X | | | | | |
| **Medical and Surgical History** | X | X[3] | | | | |
| **Laboratory Assessment for Pregnancy** | X | | | | | |
| **Wound Assessments** | X | X[4] | X | X | X | X |
| **Bedside Eschar Debridement (if needed)** | | X | | | | |
| **Initial Treatment Application** | | X | | | | |
| **Dressing Change** | | | X[5] | X[5] | | X[5] |
| **Dressing Removal** | | | | | X | X[6] |
| **3D Imaging** | | X[4] | X | X | X | X |
| **End of Study** | | | | | X | X[6] |
| **Concomitant Medication** | | X | X | X | X | X |
| **Adverse Events** | | X | X | X | X | X |

[1] Visit should not occur prior to 48 hours from the previous visit.
[2] Inclusion/Exclusion Criteria will be reconfirmed immediately prior to randomization if Visit 1 and Visit 2 are on different dates.
[3] If the screening visit and randomization occur on different days, the medical and surgical history will be updated (if changes have occurred).
[4] For patients undergoing eschar debridement prior to randomization, the procedure is performed before and after debridement (see Section 4.10).
[5] Dressing changes can occur daily for patients randomized to the collagenase ointment group (or more frequently if dressings become soiled).
[6] If the Subject is withdrawn early.

### 3.3. Randomization

Subjects who meet all inclusion criteria and no exclusion criteria will be randomized in a 1:1 ratio to either the VFCC and NPWTi-d arm or the collagenase ointment treatment arm. The randomization will be stratified for the clinical site using permuted blocks to achieve equal numbers of Subjects assigned to the treatment groups within each clinical site.

A randomization schedule, including randomization numbers and treatment assignments, will be generated and maintained centrally in a web-based clinical database management system. Once randomized, a Subject's assignment cannot be altered or changed; a Subject should not be randomized more than once.

The randomization schedule should only be visible to the study statisticians and clinical database study builders. In the circumstance of exposure of the randomization schedule to any other personnel, a new schedule will be generated for all future Subjects, which may break the original balance in each block, i.e., site.

### 3.4. Blinding

This is an open-label study so blinding of protocol-assigned product use at the clinical sites could not occur.

Prior to the planned interim analysis and prior to the finalization of the interim and final SAPs, any programming of the raw data was stripped of the actual treatment assignment and a dummy treatment assignment used instead. This ensured blinding of interim results during SAP and program development.

The independent assessor is blinded to the treatment assignment when examining the wound images for area, volume and tissue typing.

## 4. STUDY ENDPOINT(S)

### 4.1. Efficacy Endpoints

#### 4.1.1. Primary Efficacy Endpoint(s)

The primary endpoint is the change in the percent of wound bed surface area considered to be clean, healthy, and viable (%) from baseline to Day 6-9 upon the final dressing removal.

#### 4.1.2. Secondary Efficacy Endpoint(s)

The secondary endpoints for this study include:

- The change in percent of wound bed surface area considered to be clean, healthy, viable tissue (%) at interim study visits (Day 2-3 day and Day 4-6).
- Percent change in total wound volume (%) from baseline to Day 6-9 upon the final dressing removal.

- The percent change in total wound volume (%) at interim study visits (Day 2-3 day and Day 4-6).
- Percent change in total wound area (%) from baseline to Day 6-9 upon the final dressing removal.
- The percent change in total wound area (%) at interim study visits (Day 2-3 day and Day 4-6).
- Within-VFCC-treatment changes in the percent of wound bed surface area considered clean, healthy, viable tissue (%) at the Day 6-9 study visit relative to baseline.
- Within-VFCC-treatment changes in the percent of total wound area (%) at the Day 6-9 study visit relative to baseline.
- Within-VFCC-treatment changes in the percent of wound volume (%) at the Day 6-9 study visit relative to baseline.
- Physician assessment of the need for surgical debridement upon completion of study treatment up to Day 6-9.

### 4.1.3. Exploratory Endpoint(s)

The exploratory endpoints for this study include:

- Repeated measures of the change in percent of clean, healthy, viable tissue (%) over time, analyzing the rate of change and differences at study visits.
- Repeated measures of the percent change in total wound volume (%) over time, analyzing the rate of change and differences at study visits.
- Repeated measures of the percent change in total wound area (%) over time, analyzing the rate of change and differences at study visits.
- The absolute change from baseline to Day 6-9 upon the final dressing removal in the wound bed surface area ($cm^2$) considered to be clean, healthy, and viable.
- The absolute change from baseline to Day 6-9 in the total wound area ($cm^2$).
- The absolute change from baseline to Day 6-9 in the total wound volume ($cm^3$).
- Repeated measures of the absolute change in total wound volume, total wound area and viable wound area over time, analyzing the rate of change and differences at study visits.
- The percent change and absolute change of granulation tissue from baseline to Day 6-9 upon the final dressing removal
- Number of treatment applications and/or dressing changes per Subject (i.e., collagenase ointment applications versus VFCC applications); analyzed by treatment duration, wound size, and/or wound type, as appropriate.
- Total time to perform treatment applications and/or dressing changes per Subject; analyzed by wound size and/or wound type, as appropriate.
- Within-VFCC-treatment changes in the percent of wound bed surface area considered clean, healthy, viable tissue (%) at Day 2-3 and Day 4-6 study visits relative to baseline.
- Within-VFCC-treatment changes in the percent of total wound area (%) at Day 2-3 and Day 4-6 study visits relative to baseline.
- Within-VFCC-treatment changes in the percent of wound volume (%) at Day 2-3 and Day 4-6 study visits relative to baseline.

- Within-Collagenase-control-treatment changes in the percent wound surface area considered clean, healthy and viable; changes in percent wound area; and changes in percent wound volume at all study visits relative to baseline.

In addition to these exploratory endpoints, the following data will be collected from Subjects in one of the groups:

- Total number of collagenase ointment tubes used per Subject; analyzed by treatment duration, wound size, and/or wound type, as appropriate.
- Number of blockage and leak alarms (obtained from the V.A.C.ULTA™ Therapy Unit log)

### 4.2. Safety Endpoint(s)

The safety endpoint for this study is the incidence of adverse event(s) (AEs). All AEs will be coded using the MedDRA coding dictionary version 22.0 or higher.

## 5. ANALYSIS POPULATIONS

The following analysis sets are planned for this study (see Table 2 for a complete comparison of these analysis sets):

**Table 2: Comparison of Different Analysis Sets**

| | Consented | Randomized | Treated by Either Arm | Analyzed as Treated | Analyzed as Randomized | Eligibility Met | Met Wound Criteria* | Had Primary Endpoint Assessment on Day 6-9 | No Disqualifying** Protocol Deviations |
|---|---|---|---|---|---|---|---|---|---|
| Safety Analysis Set (SAS) | ✓ | | ✓ | ✓ | | | | | |
| Intention to Treat Analysis Set (ITT)/Full Analysis Set (FAS) | ✓ | ✓ | | | ✓ | | | | |
| Modified Intention to Treat Analysis Set (mITT) | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | |
| Per-Protocol Analysis Set (PP) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

* Has no more than 2/3 of the wound bed surface area considered to be clean, healthy, viable wound bed as determined at the baseline measurement confirmed with 3D images by an independent assessor

** No disqualifying protocol deviation(s) or missing primary endpoint data that would impact the interpretation/analysis of the primary endpoint

### 5.1. Safety Population

Safety Analysis Set includes all randomized Subjects who received either VFCC and NPWTi-d or collagenase ointment for any length of time. Subjects will be analyzed as treated.

### 5.2. Intent-To-Treat Population

The intent-to-treat (ITT) analysis set includes all randomized Subjects. Subjects will be analyzed as randomized.

### 5.3. Full Analysis Set

The Full Analysis Set (FAS) will be defined as all randomized Subjects who have received treatment, either VFCC and NPWTi-d or collagenase ointment for any length of time. Subjects will be analyzed as randomized. See Section 6.3.1 on situations where missing data will be imputed in the FAS.

### 5.4. Modified Intention-to-Treat Population (mITT)

Modified intent-to-treat (mITT) will include all randomized Subjects with the following:

i. met all the inclusion criteria and none of the exclusion criteria,
ii. had no more than 2/3 of the wound bed surface area considered to be clean, healthy, viable wound bed as determined at the baseline measurement confirmed with 3D images by an independent assessor,
iii. received either the V.A.C. VERAFLO CLEANSE CHOICE™ Dressing and NPWTi-d or collagenase ointment,
iv. had the primary endpoint assessment on Day 6-9

### 5.5. Per-Protocol Population

Per-Protocol (PP) analysis set will include all Subjects in the mITT who had no disqualifying or major protocol deviation(s) that would impact the interpretation of the primary endpoint (i.e. change in percent of wound surface area considered clean, healthy and viable). Subject data will be analyzed in the arm to which they were randomized and treated.

Situations and deviations that lead to an exclusion from the PP analysis will be defined and justified in a blinded fashion. In addition, documentation will be made of these data classification decisions prior to database lock.

## 6. GENERAL STATISTICAL CONSIDERATIONS

- Data processing, tabulation of descriptive statistics and calculation of inferential statistics will be performed primarily using SAS version 9.4 or higher (SAS Institute, Cary, NC). If the use of other software is warranted, the final report will detail software deployed along with the reasons for use.

- Summaries of continuous variables will show the number of non-missing values [n], along with the mean, standard deviation, median, minimum, and maximum. In general, minimum and maximum 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. Standard deviation

and confidence interval limits will be presented to two decimal places more than the raw data.

- Summaries of categorical (qualitative) variables will include the frequency and percentage of Subjects in each category. In general, the denominator for the percentage calculation will be based upon the total number of Subjects in the study population, unless otherwise specified. Percentages will be presented to 1 decimal place, except a value of zero, which will only be displayed as "0" or unless otherwise specified.
- Subjects in all the analysis sets will be summarized by treatment arm and overall.
- P-values will be presented to four decimal places. A p-value less than 0.0001 will be presented as < 0.0001 or < .0001.
- The assessment prior to the initial treatment application will be considered a baseline value. If debridement is deemed to be necessary, then the assessment directly after debridement will be used as the baseline reference.
- Percent change from baseline will be calculated using the relevant post initial dressing application value minus the baseline value.

Other ad hoc data analyses may be conducted to characterize the activity of the treatment. These additional ad hoc analyses will be decided at the time of the analysis and will be identified in the output and CSR. Other ad hoc data analyses to characterize safety and/or efficacy activity of treatment arms may be conducted. These additional ad hoc analyses will be decided at the time of analysis and will be labeled as such. Due to the exploratory nature of the analyses, no adjustment for multiplicity will be made in these ad hoc analyses.

## 6.1. Interim Analysis

A non-binding, unblinded interim analysis will be performed when approximately 30 evaluable Subjects have had their assessments for the primary endpoint (percent change on wound bed surface area considered to be clean, healthy, and viable from baseline to Day 6-9). The purpose of the interim analysis is to evaluate the need for early stopping due to futility, efficacy, and/or sample size re-estimation.

Details of the planned analyses to occur at interim are outlined in the interim Statistical Analysis Plan (SAP) document: CLIN-PROT-SAP-05-813629.

## 6.2. Determination of Sample Size

The study will randomize approximately 60 Subjects from approximately 15 sites in a 1:1 ratio to either the V.A.C. VERAFLO CLEANSE CHOICE™ (i.e., Treatment) arm or the collagenase ointment (i.e., Control) arm. Sample size determination is based on the primary endpoint. It was estimated that slough reduced by almost 20% in the Tender Wet 24 group and 10% in the Iruxol N group in M. Konig et al.[1] Assuming a 20% increase in clean, healthy, viable wound bed surface area in the collagenase ointment group and a 40% increase in clean, healthy, viable wound bed surface area in the VFCC and NPWTi-d group, and a typical standard deviation of 22%, 23

evaluable Subjects per group would provide approximately 80% power to detect a statistically significant difference using the Wilcoxon Rank-Sum test (nQuery Advisor® 7.0).

In some circumstances, even though the investigator assessed the wound to have ≤ 2/3 area of clean, healthy, and viable wound bed, it may not meet the requirement when assessed by the independent assessor if measured by a 3D camera. Such Subjects will be excluded from the mITT for the analysis of the primary endpoint. To allow for this possibility, plus the possibility that some Subjects may be lost to follow-up prior to their post-baseline assessment at the Day 6-9 visit, the sample size is increased to a total of 60 randomized Subjects (i.e., 30 Subjects per arm). This accounts for an approximately 23% drop out rate.

## 6.3. Handling of Dropouts and Missing Data

### 6.3.1. Imputation for Missing Efficacy and General Data

Missing efficacy data will not be imputed in the primary analysis on the changes in percent wound bed considered clean, healthy, viable tissue (%) using the mITT dataset.

Missing efficacy data involving the primary and secondary endpoints using the FAS dataset will be imputed using the next observation carried backward (NOCB) for missing baseline data and last observation carried forward (LOCF) for missing post-baseline data. Data will be imputed for the FAS dataset that are missing for the following variables: percent wound area considered clean/viable/healthy; wound area; and wound volume. The derived endpoints impacted will be change in percent of wound bed considered clean, healthy, viable tissues (%), percent change in wound area (%), percent change in wound volume (%), absolute change in total area ($cm^2$), absolute change in area considered clean, viable, healthy ($cm^2$), and absolute change in volume ($cm^3$). This dataset will be referred to as FAS (with NOCB/LOCF imputation).

The secondary endpoint of Physician assessment of the need for surgical debridement upon completion of study treatment up to Day 6-9 implies that assessment made prior to Day 6-9 (even on unscheduled visits) reflecting the end-of-treatment assessment will be used. In the event that this secondary endpoint or any exploratory endpoint (except the absolute change in total area, volume, and area considered clean, viable, healthy) is missing, imputation will not be carried out and all available data will be used in the analysis. All available data without imputation will be referred to as ITT (without imputation).

If wound type was missing prior to protocol version 5.0 (when I/E criteria was modified to broaden the wound types allowed in the study), the wound type will be set to “Pressure Ulcer”.

Wounds with no undermining will have the percent of wound margin with undermining set to 0%. In addition, percent of wound margin with undermining initially captured as <25% will be summarized in the report as 1-<25% for clarity.

### 6.3.2. Conventions/Imputations for Adverse Events and Concomitant Medications.

If the adverse event (AE)/ Concomitant Medication (CM) start date is partially missing [e.g. the month of the start date is missing, or the day of the date is missing], the following conventions will be applied:

- If only the day is missing then the imputed day will be: The day of the initial dressing/treatment application if the month is the same, or the first day of the month will be used if the month differs or the imputed day results in a start date after the end date.
- If only the month is missing then the imputed month will be the month of the initial dressing/treatment application if the year is the same, or 'January' if the year differs.
- If both month and day are missing, then the month is imputed as the month and day of the initial dressing/treatment application. If the imputed day results in a start date after the end date, then the first day of the month will be used.

If the AE start date is missing and the end date is complete

- If the end date is on or after the date of the initial dressing application/treatment, the start date will be imputed as the date of the initial dressing application/treatment start.
- If the start date is completely missing and the end date is completely missing then the AE/CM will assume to be "on-study", then the start date will be set to the date of the initial dressing application/treatment.
- If the start date is completely missing and end date is prior to the initial dressing application/treatment, the AE/CM will assume to be 'prior to study' and not be included in any summaries.

## 6.4. Validation Plan

Level 2 validation plan will be implemented for programs creating the STDM and ADaM datasets and at least level 1 for output programs.

# 7. SUMMARY OF STUDY POPULATION

## 7.1. Subject Disposition

The disposition summary will include the following:

- All Subjects who provided informed consent.
- All Subjects who failed screening along with the reasons.
- All Subjects in the ITT analysis set
  - Number and percentage of study completion and early discontinuation.
  - Number and percentages of reasons for early discontinuation. Percentages are based on the ITT analysis set.
- All Subjects in the Safety analysis set.
- All Subjects in the mITT analysis set.
- All Subjects in the FAS analysis set.

- All Subjects in the Per-Protocol (PP) analysis set.
- Reasons for Subjects excluded from the mITT, FAS, and Per-Protocol (PP) analysis sets. Percentages are based on the ITT analysis set.

A consort diagram describing Subject enrollment and disposition will be provided. Reasons for Subjects excluded from the mITT analysis set include: not meeting the inclusion/exclusion criteria; area of clean, healthy, and viable wound bed is greater than 2/3 of the wound bed surface area; did not receive any treatment; or did not have the primary endpoint assessment on Day 6-9. Reasons for Subjects excluded from the PP analysis set also include having protocol deviations that impacts the primary analysis.

## 7.2. Clinical Investigation Plan Deviations

Protocol deviations will be defined as departures from the study protocol that could potentially affect clinical results or safety conclusions. All protocol deviations will be identified, recorded, and presented in Subject data listings.

The clinical study team will review the protocol deviation data and identify and document all disqualifying protocol deviations prior to the final database lock. All disqualifying protocol deviations for the PP analysis set will be presented in listings and will be summarized by coded term/description based on the ITT analysis set.

## 7.3. Baseline and Demographic Characteristics

Demographics, baseline characteristics and treatment compliance will be presented by treatment arm, and based on the overall mITT, FAS, and PP analysis sets.

Medical history summaries will be presented by treatment arm and overall using the FAS, and mITT populations.

### 7.3.1. Demographics

Baseline demographics and other characteristics (e.g., age, sex, race, ethnicity, height, weight, body mass index (BMI)). Age and BMI will be compared between the treatment arms using a two-sample t-test (Wilcoxon sum rank test will be used instead if distribution is significantly skewed). Race/ethnicity and sex will be compared between the treatment arms using Fisher's exact test as appropriate.

### 7.3.2. Baseline Characteristics

Baseline wound assessment by the investigator, which includes the need for bedside eschar debridement along with the debridement type, wound length, width, and estimated percentage of clean, healthy and viable wound bed surface, wound odor, presence of undermining, depth of undermining at maximum undermined area (cm), percentage of wound margin with undermining present.

### 7.3.3. Medical History

Baseline comorbidities will be summarized and compared between the two treatment arms using Fisher's exact test as appropriate.

All captured medical history, which will be coded using a MedDRA coding dictionary version 23.0 or higher, will be summarized by System Organ Class and Preferred Term based on the FAS and mITT analysis set. Incidence of medical history that can impact wound healing will also be provided, which includes diabetes, peripheral vascular disease, COPD, anemia, local/systemic infection, cancer, poor nutrition, and aging, etc.

## 7.4. Treatment/Device Use Duration and Compliance

Treatment duration will be computed as the number of days from randomization to the last treatment day: (Last Treatment Date-Randomization Date +1). If the last treatment date is missing, the day of last study visit will be used. Testing for differences between the two treatment arms will be carried out using a two-sample t-test (Wilcoxon sum rank test will be used instead if distribution is significantly skewed).

Treatment duration, number of treatment applications and/or dressing changes per Subject will be summarized by treatment group (collagenase ointment and VFCC) and overall.

Treatment duration will be computed as the number of days from randomization to the last treatment day: (Last Treatment Date-Randomization Date +1).

# 8. EFFICACY ANALYSIS

## 8.1. Primary Efficacy Analysis

The primary endpoint is the change in the percent of wound bed surface area ($cm^2$) considered to be clean, healthy, and viable from baseline to Day 6-9 upon the final dressing removal. The percentage of clean, healthy, and viable tissue (pctCHV) is defined as the sum of percentages of viable Bone/Cartilage/Ligament/Tissue (B/C/L/T), viable fat, viable muscle/fascia, and granulation tissue. The change in percent (ΔpctCHV) of clean, healthy, and viable tissue from baseline to Day 6-9 upon the final dressing removal is defined as:

$$\Delta pctCHV = pctCHV4 - pctCHV0$$

where,
pctCHV0 = percent of clean, healthy, and viable tissue at baseline
pctCHV4 = percent of clean, healthy, and viable tissue at Day 6-9 upon final dressing removal.

The following hypothesis will be tested:

Null: $\Delta pctCHV_{VFCC} - \Delta pctCHV_{Control} = 0$ Alternative: $\Delta pctCHV_{VFCC} - \Delta pctCHV_{Control} \neq 0$

where $\Delta pctCHV_{VFCC}$ - $\Delta pctCHV_{Control}$ is the difference of the change in percent of wound bed surface area ($cm^2$) considered to be clean, healthy, and viable between the VFCC with NPWTi-d group and the Control group.

Generalized linear modeling will be used to analyze the primary endpoint with the following fixed effects: clinical site; baseline percent of wound bed surface considered clean, healthy and viable [pctCHV0]; body mass index [BMI]; treatment arm and indicator of baseline wound undermining.

If any of the covariates (except treatment arm and site ID) is not statistically significant at the 0.1 level, then the non-significant term(s) will be removed from the model and the updated model will be re-run. The analysis will be conducted at the α-level determined by the O'Brien-Fleming α-spending function[2] and observed fraction time.

```
proc mixed data=adeff;
     class trtp siteid undermin;
     model chg=bmi base trtp siteid undermin / ddfm=kr cl;
     lsmeans trtp/ diff cl;
run;
```

The analysis will be conducted at a final alpha level as determined by the O'Brien-Fleming α-spending function[2]. The primary analysis will be based on the mITT analysis set, and the test of the difference of the least square means estimates.

Additionally, a line plot and/or scatterplot and/or boxplots showing the mean or observed percentage in the wound bed surface area considered to be clean, healthy, and viable by treatment arm over time will be generated to display the results from the analyses of the primary endpoint in the FAS, mITT and PP analysis sets.

The following supportive analyses will be conducted in the primary endpoint:

- Repeat the primary analysis on the FAS analysis set using Next Observation Carried Back (NOCB) and Last Observation Carried Forward (LOCF) method, that is, FAS (with NOCB/LOCF imputation).
- Repeat the primary analysis on the Per-Protocol analysis set

If appropriate, supportive/exploratory analyses of the primary endpoint will include:

- A proportional odds logistic regression model (ordered logit link function) with quartile or quintile groupings of the data
- Wilcoxon Rank-Sum test without adjusting for covariates like wound undermining
- Analyses comparing the treatment groups considering covariates (e.g., age, race/ethnicity, sex, and comorbidities)
- Other analyses deemed appropriate to examine unexpected interaction terms including, but not limited to, impact of the Covid pandemic.

## 8.2. Secondary Efficacy Analysis

The secondary efficacy analyses will be conducted to ensure that the family-wise error rate is controlled using the Holm method for multiplicity adjustment. The following are the relevant secondary analyses of interest:

(Between-Treatment Testing)

1. The change in percent of wound surface area with clean, healthy, viable tissue (%) at the Day 4-6 interim visit relative to baseline between the treatment arms.
2. The change in percent of wound surface area with clean, healthy, viable tissue (%) at the Day 2-3 interim visit relative to baseline between the treatment arms.
3. Percent change in total wound area (%) from baseline to Day 6-9 upon the final dressing removal between the treatment arms
4. Percent change in total wound area (%) from baseline to Day 4-6 between the treatment arms
5. Percent change in total wound area (%) from baseline to Day 2-3 between the treatment arms
6. Percent change in total wound volume (%) from baseline to Day 6-9 upon the final dressing removal between the treatment arms
7. Percent change in total wound volume (%) from baseline to Day 4-6 between the treatment arms
8. Percent change in total wound volume (%) from baseline to Day 2-3 between the treatment arms
9. Physician assessment of the need for surgical debridement upon completion of study treatment up to Day 6-9

(Within-Treatment Testing)

10. Within-treatment-arm changes in percent of wound surface area assessed as clean, healthy, viable tissue (%) at the Day 6-9 visit to baseline for VFCC arm.
11. Within-treatment-arm changes in percent of total wound area (%) at the Day 6-9 visit to baseline for VFCC arm.
12. Within-treatment-arm changes in percent of total wound volume (%) at the Day 6-9 visit to baseline for VFCC arm.

### 8.2.1. Change in percent of wound surface area with healthy/viable/clean tissue relative to baseline

The analysis conducted as primary analysis will be repeated for Day 4-6 and Day 2-3 results. These analyses will be carried out for the mITT and FAS (with NOCB/LOCF imputation).

### 8.2.2. Percent change in total wound area ($cm^2$) relative to baseline

The percent change in total wound area (ΔpctArea) from baseline to Day X upon the final dressing removal is defined as the difference in total wound area between the Day X assessment and baseline assessment, divided by the baseline value and multiplied by 100.

$$\Delta pctArea = \left(\frac{AreaX - Area0}{Area0}\right) \times 100$$

where,

Area0 = the total wound area at baseline

AreaX = the total wound area at Day X (e.g. Day 6-9) upon final dressing removal.

The following hypothesis will be tested:

Null: $\Delta pctArea_{VFCC} - \Delta pctArea_{Control} = 0$ Alternative: $\Delta pctArea_{VFCC} - \Delta pctArea_{Control} \neq 0$

where $\Delta pctArea_{VFCC} - \Delta pctArea_{Control}$ is the difference of percent change in total wound area ($cm^2$) between the VFCC with NPWTi-d group and Control group.

The appropriate generalized linear modeling will be used to analyze the endpoint with potential fixed effects: clinical site; baseline total wound area; body mass index [BMI]; treatment arm and indicator of baseline wound undermining. These analyses will be carried out for the mITT and FAS (with NOCB/LOCF imputation).

### 8.2.3. Percent change in total wound volume ($cm^3$) relative to baseline

The percent change in total wound volume (ΔpctVol) from baseline to Day X upon the final dressing removal is defined as the difference in total wound area between the Day X assessment and baseline assessment, divided by the baseline value and multiplied by 100.

$$\Delta pctVol = \left(\frac{VolX - Vol0}{Vol0}\right) \times 100$$

where,

Vol0 = the total wound volume at baseline

VolX = the total wound volume at Day X (e.g. Day 6-9) upon final dressing removal.

The following hypothesis will be tested:

Null: $\Delta pctVol_{VFCC} - \Delta pctVol_{Control} = 0$ Alternative: $\Delta pctVol_{VFCC} - \Delta pctVol_{Control} \neq 0$

where $\Delta pctVol_{VFCC} - \Delta pctVol_{Control}$ is the difference of percent change in total wound volume ($cm^3$) between the VFCC with NPWTi-d group and Control group.

The appropriate generalized linear modeling will be used to analyze the endpoint with potential fixed effects: clinical site; baseline total wound area; body mass index [BMI]; treatment arm and indicator of baseline wound undermining. These analyses will be carried out for the mITT and FAS (with NOCB/LOCF imputation).

### 8.2.4. Within-VFCC-Treatment Arm Testing

The appropriate generalized linear modeling will be used to analyze the primary or secondary endpoint (percent change in wound area considered clean/viable/healthy, total wound area, and wound volume) with the following potential fixed effects: clinical site; baseline total wound area; body mass index; treatment arm; and indicator of baseline wound undermining.

The within-arm testing will be based on the least square means estimate for the VFCC treatment arm derived from the final model used for the between-treatment testing in the primary or secondary analyses. These analyses will be carried out for the mITT and FAS (with NOCB/LOCF imputation).

### 8.2.5. Physician assessment of the need for debridement at end of treatment

There are two possible outcomes for this endpoint:

- "Yes", which is assigned if the Subject needed wound debridement after the completion of treatment.
- "No", which is assigned if the Subject did not need wound debridement after the completion of treatment.

Based on the mITT analysis set, the number and percentage of Subjects with each possible outcome (Yes/No) will be summarized by treatment groups (VFCC and NPWTi-d vs collagenase ointment) and overall. Fisher's exact test will be performed to evaluate the difference between the two treatment groups.
If appropriate, the analysis above will be repeated on the ITT (without imputation) and per protocol (PP) analysis sets as supportive/exploratory analyses of this secondary endpoint.

## 8.3. Exploratory Analysis

### 8.3.1. Tissue Typing Assessments

Tissue typing assessments will be summarized across timepoints by treatment arm and by visit based on the mITT and FAS (with imputation) analysis sets.

The variables to be summarized are as follows: Viable B/L/C/T (bone/ ligament /cartilage/ tendon); Viable fat; Granulation; Viable muscle/fascia; Non-viable B/L/C/T; Non-viable fat; Non-viable muscle/fascia; Eschar; and Slough. These variables will be summarized as percent of total wound surface area (%) and absolute area ($cm^2$).

The composite variables to be summarized in terms of percent of total wound surface area (%) and absolute area ($cm^2$) are:

1. clean/healthy/viable tissues (sum of the first four categories listed previously: viable B/L/C/T (bone/ligament/cartilage/tendon); viable fat; granulation; viable muscle/fascia) and
2. non-viable tissue (sum of non-viable B/L/C/T; non-viable fat; non-viable muscle/fascia; eschar; and slough).

Summaries by wound type (pressure ulcer, diabetic foot ulcer, venous leg ulcer and burn wounds) will be carried out if appropriate.

All data supporting the summaries will be provided as subject listings with all available and imputed data included.

### 8.3.2. Repeated Measures Analyses

In addition, a repeated measures analysis of covariance model (ANCOVA) will be applied to analyze the endpoints of percent of wound bed clean/viable/healthy, total wound volume and total wound area. Fixed covariates of clinical site, treatment arm, wound undermining measurement, visit, and treatment by visit. If clinical site or treatment by visit is not statistically significant, then the non-significant term(s) will be removed from the model, and the updated model will be re-run. Covariance structure will be unstructured, AR(1) or TOEFL, selected based on best fit (likelihood ratio tests or based on appropriate fit statistics).
These endpoints will be summarized based on the mITT and the FAS (with NOCB/LOCF imputation) analysis sets.

### 8.3.3. Additional Within-VFCC-Arm-Testing and Within-Collagenase-Control-Arm-Testing

The appropriate generalized linear modeling will be used to analyze the primary or secondary endpoint (percent change in wound area considered clean/viable/healthy, total wound area, and wound volume) with the following potential fixed effects: clinical site; baseline total wound area; body mass index; treatment arm; and indicator of baseline wound undermining.

The within-arm testing will be based on the least square means estimate for the VFCC or Collagenase treatment arm derived from the final model used for the between-treatment testing in the primary or secondary analyses. This exploratory testing will occur in conjunction with the within-VFCC-treatment arm testing described previously in section 8.2.4. This testing plan will examine within-VFCC and within-collagenase changes in percent wound surface area assessed as clean, healthy and viable; percent total wound area, and percent wound volume at all study visits relative to baseline. These analyses will be carried out for the mITT and FAS (with NOCB/LOCF imputation).

### 8.3.4. Absolute change in wound area ($cm^2$) considered clean/healthy/viable relative to baseline

The absolute change from baseline to Day X upon the final dressing removal in the wound bed surface area ($cm^2$) considered to be clean, healthy, and viable
This exploratory endpoint is defined as the absolute difference in the wound bed surface area ($cm^2$) considered to be clean, healthy, and viable between the Day X assessment value and baseline value. The absolute value of clean, healthy, and viable tissue in the wound bed surface area (absCHV) is defined as the percent of clean, healthy, and viable tissue (pctCHV) (defined in section 8.4) divided by 100 and multiplied by total wound area.

The absolute change from baseline to Day X upon the final dressing removal in the wound bed surface area ($cm^2$) considered to be clean, healthy, and viable is then defined as:

$$\Delta absCHV = absCHVX - absCHV0$$

where,

absCHV0 = absolute value of clean, healthy and viable tissue in the wound bed surface area ($cm^2$) at baseline

absCHVX = absolute value of clean, healthy and viable tissue in the wound bed surface area ($cm^2$) at Day X (e.g. Day 6-9) upon final dressing removal

The following hypothesis will be tested:

Null: $\Delta absCHV_{VFCC} - \Delta absCHV_{Control} = 0$ Alternative: $\Delta absCHV_{VFCC} - \Delta absCHV_{Control} \neq 0$

where $\Delta absCHV_{VFCC} - \Delta absCHV_{Control}$ is the difference in the absolute value change in the wound bed surface area ($cm^2$) considered to be clean, healthy, and viable from baseline to Day X upon the final dressing removal between the VFCC with NPWTi-d group and Control group.

The appropriate generalized linear modeling will be used to analyze the endpoint with potential fixed effects: clinical site; baseline total wound area; body mass index [BMI]; treatment arm and indicator of baseline wound undermining. If any of the covariates (except treatment arm and site ID) is not statistically significant at the 0.1 level, then the non-significant term(s) will be removed from the model and the updated model will be re-run. These endpoints will be summarized based on the mITT and FAS (with NOCB/LOCF imputation) analysis sets.

### 8.3.5. The absolute change in the total wound area ($cm^2$) relative to baseline

This exploratory endpoint is defined as the absolute difference in wound area between the Day X assessment value and baseline value:

$$\Delta absArea = AreaX - Area0$$

where,

Area0 = the total wound area at baseline

AreaX = the total wound area at Day X (e.g. Day 6-9) upon final dressing removal.

The following hypothesis will be tested:

Null: $\Delta absArea_{VFCC} - \Delta absArea_{Control} = 0$ Alternative: $\Delta absArea_{VFCC} - \Delta absArea_{Control} \neq 0$

where $\Delta absArea_{VFCC} - \Delta absArea_{Control}$ is the absolute difference in the total wound area from baseline to Day X upon final dressing removal between the VFCC with NPWTi-d group and Control group.

The appropriate generalized linear modeling will be used to analyze the endpoint with potential fixed effects: clinical site; baseline total wound area; body mass index [BMI]; treatment arm and indicator of baseline wound undermining. If any of the covariates (except treatment arm and site

ID) is not statistically significant at the 0.1 level, then the non-significant term(s) will be removed from the model and the updated model will be re-run. These endpoints will be summarized based on the mITT and FAS (with NOCB/LOCF imputation) analysis sets.

### 8.3.6. The absolute change in the total wound volume ($cm^3$) relative to baseline

This exploratory endpoint is defined as the absolute difference in wound volume between the Day X assessment value and baseline value:

$$\Delta absVol = VolX - Vol0$$

where,

Vol0 = the total wound volume at baseline

VolX = the total wound volume at Day X (e.g. Day 6-9) upon final dressing removal.

The following hypothesis will be tested:

Null: $\Delta absVol_{VFCC} - \Delta absVol_{Control} = 0$ Alternative: $\Delta absVol_{VFCC} - \Delta absVol_{Control} \neq 0$

where $\Delta absVol_{VFCC} - \Delta absVol_{Control}$ is the absolute difference in the total wound volume from baseline to Day X upon final dressing removal between the VFCC with NPWTi-d group and Control group.

The appropriate generalized linear modeling will be used to analyze the endpoint with potential fixed effects: clinical site; baseline total wound area; body mass index [BMI]; treatment arm and indicator of baseline wound undermining. If any of the covariates (except treatment arm and site ID) is not statistically significant at the 0.1 level, then the non-significant term(s) will be removed from the model and the updated model will be re-run. These endpoints will be summarized based on the mITT and FAS (with NOCB/LOCF imputation) analysis sets.

### 8.3.7. The percent change of granulation tissue (%) relative to baseline

This exploratory endpoint is defined as the percent difference of viable granulation tissue between Day X and baseline:

$$\Delta pctGra = GranulationX - Granulation0$$

where,

Granulation0 = percent of granulation tissue (%) at baseline as assessed by independent assessor

GranulationX = percent of granulation tissue (%) at Day X (e.g. Day 6-9) upon final dressing removal as assessed by independent assessor.

The following hypothesis will be tested:

Null: $\Delta pctGra_{VFCC} - \Delta pctGra_{Control} = 0$ Alternative: $\Delta pctGra_{VFCC} - \Delta pctGra_{Control} \neq 0$

where $\Delta pctGra_{VFCC} - \Delta pctGra_{Control}$ is the percent difference of granulation tissue from baseline to Day X upon final dressing removal between the VFCC with NPWTi-d group and Control group.

The appropriate generalized linear modeling will be used to analyze the endpoint with potential fixed effects: clinical site; baseline total wound area; body mass index [BMI]; treatment arm and indicator of baseline wound undermining. If any of the covariates (except treatment arm and site ID) is not statistically significant at the 0.1 level, then the non-significant term(s) will be removed from the model and the updated model will be re-run. These endpoints will be summarized based on the ITT (with no imputation) analysis sets.

### 8.3.8. The absolute change of area covered with granulation tissue ($cm^2$) relative to baseline

This exploratory endpoint is defined as the difference in the absolute value of viable granulation tissue between Day X and baseline, where the absolute value of viable granulation tissue is the percent of viable granulation tissue divided by 100 and multiplied by total wound area:

$$\Delta absGra = \frac{AreaX \times GranulationX - Area0 \times Granulation0}{100}$$

where,

Area0 = the total wound area at baseline

AreaX = the total wound area at Day X (e.g. Day 6-9) upon final dressing removal.

Granulation0 = percent of granulation tissue (%) at baseline as assessed by independent assessor

GranulationX = percent of granulation tissue (%) at Day X (e.g. Day 6-9) upon final dressing removal as assessed by independent assessor.

The following hypothesis will be tested:

Null: $\Delta absGra_{VFCC} - \Delta absGra_{Control} = 0$ Alternative: $\Delta absGra_{VFCC} - \Delta absGra_{Control} \neq 0$

where $\Delta absGra_{VFCC} - \Delta absGra_{Control}$ is the difference of the absolute value of granulation tissue from baseline to Day X upon final dressing removal between the VFCC with NPWTi-d group and Control group.

The appropriate generalized linear modeling will be used to analyze the endpoint with potential fixed effects: clinical site; baseline total wound area; body mass index [BMI]; treatment arm and indicator of baseline wound undermining. If any of the covariates (except treatment arm and site ID) is not statistically significant at the 0.1 level, then the non-significant term(s) will be removed from the model and the updated model will be re-run. These endpoints will be summarized based on the ITT (with no imputation) analysis set.

### 8.3.9. Treatment Application Characteristics

The endpoints below will be summarized as appropriate in reference to Section 7.1 in either the VFCC with NPWTi-d group or Control group based on the Safety analysis sets.

Total number of collagenase ointment tubes used per Subject, summarized as the number of all new tubes used for each Subject by visit and the total new tubes used from baseline to Day 6-9 upon dressing removal.

Other treatment application characteristics, such as system leaks and additional drapes used in the VFCC with NPWTi-d group and tube size, SOC dressing type, and whether the dressing contains an antimicrobial or cleanser in the Control group.

Number of blockage and leak alarms (obtained from the V.A.C.ULTA™ Therapy Unit log), summarized as the number of all blockage and leak alarms recorded in the V.A.C.ULTA™ Therapy Unit log for each Subject by visit and the total number of blockage and leak alarms from baseline to Day 6-9 upon dressing removal.

The endpoints below will be listed in the VFCC with NPWTi-d group based on the Safety analysis set:

• # of System Fault Alarms per patient (overall and per day)

• # of Battery Critical Alarms per patient (overall and per day)

• # of V.A.C. VeraFloTM Blockage Alerts per patient (overall and per day)

• # of V.A.C. VeraFloTM Low Pressure Alarms per patient (overall and per day)

• # of V.A.C. VeraFloTM Therapy Blockage Alarm – Therapy Interrupted per patient (overall and per day)

• #V.A.C. VeraFloTM Low Pressure Alarms/#V.A.C. VeraFloTM Blockage Alerts % per patient (overall and per day): this is the percentage of time initial alert was not managed appropriately and turned into an alarm

• #V.A.C. VeraFloTM Therapy Blockage Alarm – Therapy Interrupted/#V.A.C. VeraFloTM Blockage Alerts % per patient (overall and per day): this is the percentage of time initial alert was not managed appropriately and turned into a therapy interrupted alarm

• # of V.A.C. VeraFloTM Leak Alarms per patient (overall and per day)

• # of V.A.C. VeraFloTM Leak Alarm – Therapy Interrupted per patient (overall and per day)

• #V.A.C. VeraFloTM Leak Alarm – Therapy Interrupted/#V.A.C. VeraFloTM Leak Alarms % per patient (overall and per day): this is the percentage of time initial alarm was not managed appropriately and turned into a therapy interrupted alarm

• # of VeraFloTM Therapy Blockage Alert's per patient (overall and per day)

The exploratory endpoints below will be summarized and compared between the VFCC with NPWTi-d group and Control group based on the Safety analysis sets using the Wilcoxon Rank-sum test.

• Total time to perform treatment applications and/or dressing changes per Subject, defined as the difference between start time and end time for treatment application or dressing change.

# 9. SAFETY ANALYSIS

## 9.1. Laboratory Tests

Pregnancy test results will be presented in listings only.

## 9.2. Adverse Events

All treatment-emergent adverse events (TEAEs), which are defined as adverse events with onset or worsening of pre-existing conditions on or after the initial dressing application through the course of the study, will be summarized. The number and percentage of treated Subjects who experienced at least one adverse event in each system organ class by preferred term will be summarized. In any given category (e.g., system organ class or preferred term), a Subject will be counted only once. The denominator for the calculation of percentages will be the number of Subjects in the Safety analysis set. The test for significant between-treatment differences will be carried out using the Fisher's exact test.

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

- Overview of all treatment-emergent adverse events (TEAEs)
- Incidence of all treatment-emergent adverse events (TEAEs) by system organ class and preferred term
- Incidence of all treatment-emergent adverse events (TEAEs) by system organ class, preferred term, and maximum severity
- Incidence of all serious adverse events (SAEs) by system organ class and preferred term
- Incidence of treatment-related TEAEs by system organ class and preferred term
- Incidence of treatment-related TEAEs by system organ class, preferred term, and maximum severity
- Incidence of treatment-related serious adverse events (SAEs) by system organ class and preferred term
- Incidence of most common >5% TEAES in any one treatment group by preferred term only
- Listing of all treatment-related adverse events
- Listing of all treatment-related serious adverse events (SAEs)
- Listing of discontinuations: Subjects who discontinued from the study due to any adverse event
- Listing of deaths: Subjects who died of any cause during the study

### 9.3. Other Safety Variables

Concomitant medications/therapies are defined as medications taken from the time of treatment application (Day 0 through the final visit). The WHO Drug Dictionary released MAR2019 or later will be used for the coding of medications.

The number of Subjects using concomitant medications will be summarized using the pharmacological subgroup name (ATC3) and preferred drug name based on the WHO Drug medical coding dictionary. In any given category (e.g., ATC3 or preferred drug name), a Subject will be counted only once. All Subjects in the Safety analysis set will be accounted for in the summation. Listings for concomitant medications will be presented by Subject. The test for significant between-treatment differences will be carried out using the Fisher's exact test.

## 10. CHANGES FROM PLANNED ANALYSIS

In Section 8.3.5.3 of the study protocol, it states that, if appropriate, supportive/exploratory analyses of the secondary endpoint "Physician assessment of the need for debridement" may include:

- repeat the analysis above on the ITT and Per protocol analysis sets
- analyses comparing the treatment groups considering covariates (e.g., age, BMI, race/ethnicity, sex, wound undermining, and co-morbidities) and subsets of the data
- analyses comparing the heterogeneity of the treatment groups across clinical sites.

In Section 8.2.5 of this SAP, it states that "if appropriate, the analysis above will be repeated on the ITT (without imputation) and Per-Protocol analysis sets as supportive/exploratory analyses of this secondary endpoint." as the other two analyses are expected to have minimal difference between the two treatment groups therefore are at risk for being deemed unnecessary and being removed.

Added other secondary and exploratory endpoints with corresponding analyses. See Section 12 Revision History for details on changes from previously planned analyses.

## 11. REFERENCES

1. ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999. http://www.amstat.org/about/ethicalguidelines.cfm

2. RSS. (1993) The Royal Statistical Society: Code of Conduct, April 1993. http://www.rss.org.uk/main.asp?page=1875.

3. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.

## 12. REVISION HISTORY

The purpose of this appendix is to describe modifications made to this document. The final SAP V1.0 was written using a legacy KCI template and approved via DocuSign on 03August 2020. The changes described below cover the conversion to the current 3M SAP template and other changes to the content of the original document.

| **Revision History Table** | | |
|---|---|---|
| **Ver-sion #** | **Description of change including section number impacted** | **Reason for change** |
| 1 | Release | Initial Version |
| 1 | Deleted appendix that detailed the planned Tables, Listings and Figures (TLFs) for the final study report. | Copied planned TLFs into a separate word document. This is a communication tool for the biostatistician, statistical programmer, and other stakeholders that is not needed in ENOVIA. |
| 1 | Section 3.4 Blinding covers the blinding of independent assessor in assessing wound images and blinding of the biostatisticians and programmer prior to interim analysis. | Document all blinding occurring in this study. |
| 1 | Section 4.1.1 Modified the primary endpoint statement from: "**percent change** in the wound bed surface area ($cm^2$) considered to be clean, healthy, and viable from baseline to Day 6-9 upon the final dressing removal" to the following: **"change in the percent** of wound bed surface area ($cm^2$) considered to be clean, healthy, and viable from baseline to Day 6-9 upon the final dressing removal". | We not computing a percent change but computing a difference or change in the derived percent of wound surface area considered clean, healthy, and viable. |
| 1 | Section 4.1.2 Added the following endpoints:<br>change in percent of clean, healthy viable tissues, and percent change in total wound area and wound volume at interim visits relative to baseline, and not just at end of study (Day 6-9) relative to baseline.<br>Added within-VFCC-treatment arm testing at 6-9 day visit relative to baseline for the same endpoints we are testing for between-treatment-arm differences. | To evaluate potential differences detected at interim visits (Day 2-3 and Day 4-6); and to evaluate potential differences of within-VFCC-arm testing. |
| 1 | Section 4.1.3 Added exploratory analysis on using repeated measures analyses of the primary and secondary endpoints; | To add important detail to account for |

| Revision History Table | | |
|---|---|---|
| **Ver-sion #** | **Description of change including section number impacted** | **Reason for change** |
| | and the previously stated exploratory endpoints (absolute changes in area considered clean/healthy/viable, total wound area and total wound volume).<br>Added within-Collagenase-control arm testing as an exploratory analysis, like the within-VFCC-testing added as secondary analyses.<br>Added Tissue Typing Assessment section that describes summary of components of the tissue analysis which include the breakdown of bone/ligament/cartilage/tendon, muscle/fascia, granulation, eschar, slough, and fat. | comprehensive and/or relevant testing. |
| 1 | Section 4.2 Safety Endpoint. Corrected the version of MedDRA dictionary to be used, from version 23.0 or higher to version 22.0 or higher. | Made correction to version of MedDRA dictionary in use. |
| 1 | Section 5 Analysis Sets. Defined another analysis set called the Full Analysis Set (FAS) as all subjects who are randomized and who received treatment. | This is supported as a valid analysis set in the E9 Guidance document, and ensures all subjects in this set can have their missing efficacy variables imputed. |
| 1 | Section 6.1 Interim Analysis removed alpha level for stopping criteria and referred to the interim SAP for details. | To better document changes to the interim analysis plan. |
| 1 | Section 6.3.1 Imputation for Efficacy and General Missing Data. Added statements on imputation rules for the primary and secondary efficacy endpoints, clarifying ITT (without imputation) and FAS (with NOCB/LOCF imputation) analysis sets. Added data handling rules for missing wound type given accepting wounds beyond Pressure Ulcer with CIP version 5 changes. | To add important detail |
| 1 | Section 6.4 Validation Plan. New section for this SAP. | To add important detail |
| 1 | Section 7.3 and Section 7.4 Added/clarified analysis populations and statistical tests for analyses on baseline, demographic characteristics, medical history, and treatment duration variables.<br>Deleted deriving a simplified wound area from investigators or site's baseline measure of width and length. | To add important details or delete inaccurate phrases, |

| Revision History Table | | |
|---|---|---|
| **Ver-sion #** | **Description of change including section number impacted** | **Reason for change** |
| | Added wound odor to the list of baseline characteristics to be summarized and tests for treatment differences. | |
| 1 | Section 8.1 Primary Efficacy Analysis. Added the option to pursue a proportional odds model if appropriate. | Accounts for the possible situation of severe violation of the normality assumption in the final linear model for the primary analysis. |
| 1 | Section 8.2 Secondary Efficacy Analysis and Section 8.3 Exploratory Analysis.<br><br>Identified 12 relevant secondary analyses of interest: three (3) within-treatment testing for the VFCC arm only and nine (9) between treatment arm testings. Outlined a Holm method of multiplicity adjustments in these secondary testing.<br><br>Changed formulas for percent change in area, percent change in volume, percent change in granulation, absolute change in area, absolute change in volume and absolute change in granulation to be consistent with primary endpoint definition such that negative values represent reductions and positive values increases with the passage of time.<br><br>Added six (6) within-VFCC tests and nine (9) within-Collagenase tests as exploratory analyses.<br><br>Modified statistical test used for categorical data analysis to Fisher's exact test rather than Chi-square or Fisher's exact test (if the sample size in any subgroup is less than 5). | To add important clarifying details |
| 1 | Section 8.3.6 and 8.3.7. Clarified the percent granulation tissue in formula is based on the percent viable granulation tissue derived from the tissue typing work done by the independent assessor from the wound images. | Clarified input variable in the formulas with percent granulation tissue. |
| 1 | Sections 9.2 and 9.3. Added statements in both sections to describe the statistical test (namely, Fisher's Exact test) to be carried out for between-treatment differences in the adverse event and medication summaries. | Specify the appropriate test for differences. |