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)

PROTOCOL NUMBER	KCI.CLEANSE.CHOICE.2017.02 NCT#: NCT03722485
SPONSOR	KCI® USA, Inc. 6203 Farinon Drive San Antonio, Texas 78249 Fax: 210.255.6760
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Study Synopsis	
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)**
PROTOCOL NUMBER:	KCI.CLEANSE.CHOICE.2017.02
TYPE AND PHASE:	A Multi-Center, Randomized, Controlled, Post-Market Open-Label Study
STUDY PRODUCT(S):	V.A.C. VERAFLO CLEANSE CHOICE™ Dressing, V.A.C.ULTA™ Therapy Unit, Normal Saline Or Collagenase ointment
STUDY OBJECTIVE(S):	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 (chronic, acute, traumatic, or dehisced wounds) and/or ulcers (ie, full-thickness wounds).
STUDY DESIGN:	This randomized, controlled, prospective multicenter study will enroll Subjects diagnosed with wounds (chronic, acute, traumatic, or dehisced wounds) and/or ulcers (ie, full-thickness wounds) 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. Subjects will receive either V.A.C. VERAFLO CLEANSE CHOICE™ Dressing and Negative Pressure Wound Therapy with instillation and dwell time (NPWTi-d; V.A.C. VERAFLO™ Therapy with saline solution) or collagenase ointment to manage their wound over a 6-9-day period. Bedside sharp and/or mechanical debridement procedures will be performed to remove eschar prior to treatment; however, sharp and/or mechanical debridement will not be performed after

	randomization during the treatment phase of the study period (up to 9 days). 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™ (ie, Treatment) arm or the collagenase ointment (ie, Control) arm after obtaining informed consent, undergoing screening procedures, and meeting all the inclusion criteria and none of the exclusion criteria. **V.A.C. VERAFLO CLEANSE CHOICE™ Dressing:** V.A.C. VERAFLO CLEANSE CHOICE™ Dressing will be applied to the wound bed and covered with drape material, providing a sealed environment for the application of NPWTi-d for a duration of 6-9 days. The dressing will be applied on Day 0 and changed twice during the treatment period, allowing at least 48 hours between each dressing change. The first dressing change will occur on Day 2-3, and the second dressing change will occur on Day 4-6. The dressing will be removed on Day 6-9 at the treatment endpoint. **Collagenase Ointment:** Collagenase ointment will be used as the control for this study as it is a commonly used option for wound cleansing. After application of the ointment, the wound will be covered with a compatible standard-of-care (SOC) dressing for up to nine (9) days. During this treatment period, the ointment can be reapplied once daily (or more frequently if the dressing requires replacement).
PRIMARY ENDPOINT:	The 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.
SECONDARY ENDPOINTS:	• Percent change in total wound volume (cm^3) from baseline to Day 6-9 upon the final dressing removal • Percent change in total wound area (cm^2) from baseline to Day 6-9 upon the final dressing removal • Physician assessment of the need for surgical debridement upon completion of study treatment up to Day 6-9
SAFETY ENDPOINT:	The safety endpoint is the Subject incidence of adverse event(s).

NUMBER OF SUBJECTS PLANNED AND DURATION OF PARTICIPATION:	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 for treatment-related adverse events that have not resolved by the final follow-up visit on Day 6-9.
NUMBER OF STUDY SITES:	This will be a multi-center study conducted at approximately 15 study sites.
INCLUSION CRITERIA:	The Subject: 1. is anticipated to be hospitalized for the duration of treatment (minimum of 6 days). 2. is ≥ 18 years of age. 3. or their legally authorized representative is able to provide informed consent. 4. has been diagnosed with a wound (chronic, acute, traumatic, or dehisced wounds) and/or ulcer (ie, full-thickness wounds) that meets the following criteria: a) total surface area measuring ≥ 16 cm^2, including a minimum width of 2 cm (before removal of eschar at the bedside and excluding undermining). b) < 20 cm across (edge-to-edge) at any point perpendicular to the wound edges. 5. has, in the opinion of the investigator, no more than 2/3 of the wound bed surface area considered to be clean, healthy, and viable. If eschar is present at baseline, it must be removed by bedside debridement prior to assessing the percentage of clean, healthy, viable wound bed. 6. has a negative urine or serum pregnancy test at screening (if female and has potential for pregnancy) and is willing to take precautionary measures to prevent pregnancy during the duration of the study (up to 9 days).
EXCLUSION CRITERIA:	The Subject: 1. has been diagnosed with a malignancy in the wound. 2. has untreated osteomyelitis. 3. has an untreated systemic infection.

	4. has active cellulitis in the periwound area. 5. has a known allergy or hypersensitivity to study materials: collagenase ointment, dressing(s), and/or dressing components such as acrylic adhesives or polyurethane. 6. has, in the opinion of the investigator, a clinically significant condition that would impair the Subject's ability to comply with the study procedures. 7. has had radiation directly to the wound area. 8. has been diagnosed with a major vascular deficit limiting arterial inflow to the wound region, as determined by the Investigator's interpretation of the Subject's medical history. 9. has eschar in the wound that cannot be removed by bedside sharp and/or mechanical debridement. 10. is participating in another interventional clinical trial for the duration of the study. 11. has unexplored fistulas in the wound or fistulas in the wound that connect to other body cavities. 12. has a wound with any tunneling present. 13. has inadequate hemostasis at the wound site, as determined by the investigator.
STUDY EVALUATION/VISIT SCHEDULE:	Visit 1: Screening within 10 Days prior to and including Day 0 Visit 2: Randomization and Study Treatment/Day 0 Visit 3: Day 2-3 Visit 4: Day 4-6 Visit 5: End of Treatment/Day 6-9
SAMPLE SIZE AND STATISTICAL METHODOLOGY:	**Analysis Sets** The *Safety Set* will consist of all consented Subjects who have received either the V.A.C. VERAFLO CLEANSE CHOICE™ Dressing and NPWTi-d or collagenase ointment for any length of time. Subjects will be analyzed as treated. The *Intent-to-Treat (ITT) Set* will consist of all randomized Subjects. Subjects will be analyzed as randomized. The *Modified Intent-to-Treat* (*mITT*) *Set* will consist of all randomized Subjects who: i) met all the inclusion criteria and none of the exclusion

	criteria ii) 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 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 The *Per-Protocol Analysis Set* will consist of Subjects in the mITT who had no disqualifying protocol deviation(s) that would impact the interpretation of the primary endpoint. The disqualifying protocol deviation(s) for exclusion from this set will be defined and documented in a blinded fashion prior to the final database lock. Subject data will be analyzed in the arm to which they were randomized and treated. **Analysis Methods** For the primary endpoint, the percent change in the wound bed surface area (cm^2) considered to be clean, healthy, and viable from baseline. The primary endpoint will be analyzed using a repeated measures analysis of covariance model (ANCOVA) with treatment arm, visit, wound undermining measurement, clinical site, and treatment by visit (Note: if clinical site or treatment by visit are not statistically significant, then the non-significant term(s) will be removed from the model and the updated model will be re-run). **Sample Size Determination** 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.[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 V.A.C. VERAFLO CLEANSE CHOICE™ Dressing and NPWTi-d, and a common standard deviation of 22%, 23 evaluable Subjects per group will provide approximately 80% power to detect a statistically significant difference using the Wilcoxon Rank-Sum test (n Query Advisor® 7.0).

	It is possible that some wounds assessed by the independent assessor will not meet the baseline requirement of no more than 2/3 area of clean, healthy, viable wound bed, as measured by a 3D camera, even though the Investigator assessed the wound at ≤ 2/3 area of clean, healthy, viable wound bed. 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 first post-baseline assessment at the Day 6-9 visit, the sample size is increased to a total of 60 randomized Subjects (ie, 30 Subjects per group).

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ACCELERATE TRIAL

SIGNATURE PAGE

Approved by: _____ Date: 14 / Feb / 2020

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Yeni Nieves, MS
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PRINCIPAL INVESTIGATOR ACKNOWLEDGEMENT OF PROTOCOL

I confirm that I have read the protocol entitled: “Hydromechanical Cleansing With V.A.C. VERAFLO CLEANSE CHOICE™ Dressing and NPWTi-d vs. Collagenase Ointment in the Management of Full-thickness Wounds” Version 5.0, dated 13 February 2020. I understand the protocol and agree to conduct the study according to the procedures therein in accordance with applicable local government regulations, institutional research policies and procedures, the Federal Drug Administration Code of Federal Regulations, the International Conference on Harmonisation principles of Good Clinical Practice, and in the spirit of the Declaration of Helsinki concerning medical research in humans.

Site Name:_____ **Site #:**_____

Principal Investigator Name: _____

Signed: _____ **Date:** _____

ABBREVIATIONS

3D	Three-dimensional
AE	Adverse event
BMI	Body mass index
CFR	Code of Federal Regulations
cm	Centimeter
cm^2	Square centimeters
CRF	Case report form
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
DFU	Diabetic foot ulcer
FDA	Food & Drug Administration
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IDE	Investigational device exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intention-to-treat
KCI®	Kinetic Concepts, Inc.
mITT	Modified intent-to-treat
mL	Milliliter
mmHg	millimeters of mercury
NP	Negative pressure
NPWT	Negative pressure wound therapy
NPWTi-d	Negative pressure wound therapy with instillation and dwell time
NSAID	Non-steroidal anti-inflammatory drug
PHI	Personal health information
RCT	Randomized controlled trial

ROCF	Reticulated open cell foam
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	Standard of care
TEAE	Treatment-emergent adverse event
UADE	Unanticipated Adverse Device Effect
US	United States
VFCC	V.A.C. VERAFLO CLEANSE CHOICE™ Dressing
VLU	Venous leg ulcer

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1. INTRODUCTION

In the United States (US), nonhealing wounds are estimated to affect approximately 2% of the general population, and impaired wound healing is conservatively estimated to have an economic impact of $25 billion to $50 billion per year to the US economy.[2;3] Nonhealing wounds are thought to be in an unresolved pro-inflammatory state, which can result in the buildup of slough (proteinaceous exudate and fibrinous tissue form).[4-6] This formation of slough along with nonviable tissue and other debris in a wound can promote an increase in bacterial bioburden, further contributing to delayed healing and wound chronicity. Therefore, a key aspect of wound management is the cleansing of wounds in order to remove slough, thick exudate, and potentially infectious materials (such as nonviable tissue) so as to obtain a clean, healthy, and viable wound bed. A major goal of wound cleansing is to clean the wound while avoiding trauma to the wound bed. Having a clean wound may help the wound progress through the inflammatory phase to the subsequent stages of healing. In fact, a clean, healthy, and viable wound bed is a necessary part of wound bed preparation so that wounds can heal, whether it be healing by secondary intention, or healing through a surgical intervention such as skin grafting, flap closure, or delayed primary intention.

1.1. Background

In the 1990s, Morykwas and Argenta introduced the use of negative pressure (NP) with a foam dressing.[7] This method has been successfully commercialized and has become a standard of care among many wound types. In 1998, Fleischman et al combined the benefits of negative pressure wound therapy (NPWT) with timed, intermittent delivery of a topical solution via gravity.[8] In 2003, KCI® commercialized the first gravity-based instillation NPWT (V.A.C. INSTILL™ Therapy) in combination with reticulated open cell foam (ROCF) into the wound healing arena. In 2010, KCI® re-engineered the product pump (V.A.C.ULTA™ Therapy Unit) to mechanically deliver the instillation solution to less hydrophobic foam dressing (V.A.C. VERAFLO™ Dressing, V.A.C. VERAFLO CLEANSE™ Dressing), which is referred to as negative pressure wound therapy with instillation and dwell time (NPWTi-d; V.A.C. VERAFLO™ Therapy; KCI®, an Acelity™

Company). The combination of instilling a topical solution over the wound bed, soaking the wound in the solution, compressing and de-compressing the foam under cycles of negative pressure, and removing the fluids via NP is a gentle method of cleansing that appears to minimize the risk of cross-contamination[9] and help decrease bacterial bioburden in the wound bed.[10] However, NPWTi-d systems have historically been limited in their ability to remove large amounts of thick exudate through the foam dressing. Recently, a novel wound interface dressing containing an array of through holes (V.A.C. VERAFLO CLEANSE CHOICE™ Dressing) has been developed that may be an important technological advancement for NPWTi-d.

1.1.1. Review of Negative Pressure Wound Therapy with Instillation and Dwell Time (NPWTi-d) and V.A.C. VERAFLO CLEANSE CHOICE™ Dressing (VFCC)

While there is broad acceptance and a large body of evidence that supports NPWT as an important tool in aiding wound healing, the evidence for NPWTi-d to improve healing has been steadily growing throughout the years. Although there are no published randomized controlled trials (RCTs) involving the use of V.A.C. VERAFLO™ Therapy found during our literature review, KCI® has recently completed a clinical study titled, “A Prospective, Randomized, Multi-Center Trial Evaluating the Effectiveness of the V.A.C.ULTA™ Negative Pressure Wound Therapy System with V.A.C. VERAFLO™ Dressing System in Operatively Debrided Wounds.” Most evidence is limited to expert opinion, case reports, abstracts, small to large case series, and a few comparative studies. These publications describe the use of NPWTi-d on a variety of wound types, including open fractures,[11] breast reconstruction,[12] necrotizing fasciitis,[11] upper and lower extremity wounds,[13] pressure ulcers,[11] venous leg ulcers (VLUs),[14] diabetic foot ulcers (DFUs),[14] and other complex wounds requiring surgical debridement.[15;16] Significant variabilities in therapeutic methods (eg, number of cycles, dwell time, volume and type of instillate) exist in the literature; however, various clinical recommendations and guidelines have been developed to guide clinicians on the use of NPWTi-d.[17-20] Furthermore, there are two (2) studies comparing NPWT to NPWTi-d.[13;15]

Since the introduction of V.A.C. VERAFLO™ Therapy, there have been several studies[13;16;21] and clinical recommendations[17-19] published on the use of instillation therapy across various wound types. However, the current literature is limited to two articles concerning NPWTi-d using V.A.C. VERAFLO CLEANSE CHOICE™ Dressing (VFCC).

Teot et al[22] retrospectively reviewed medical records from 21 patients with 21 large complex wounds that contained substantial areas of yellow, fibrinous slough who received treatment with V.A.C. VERAFLO™ Therapy using VFCC in an acute care setting. The wounds included a range of clinical situations, including difficult wounds with non-viable and/or fibrinous tissue on the wound surface. V.A.C. VERAFLO™ Therapy with VFCC was delivered by instilling normal saline with a 10-minute dwell time, followed by 3.5 hours of NP at -125 mmHg. The mean number of dressing changes was 2.9, and the mean duration of therapy was 8.7 days. V.A.C. VERAFLO™ Therapy with VFCC assisted in loosening, solubilizing, and detaching viscous exudate, dry fibrin, wet slough and other infectious materials. Wound management required an average of 1-3 VFCC dressing applications (3-9 days of V.A.C. VERAFLO™ Therapy), after which 18/21 (85.7%) wounds had ≤ 10% surface area with black non-viable tissue remaining and 12/21 (57.1%) wounds had ≤ 10% surface area with yellow fibrinous slough remaining. A total of 20/21 (95.2%) wounds displayed enhanced granulation tissue formation and reduction in wound volume during use of V.A.C. VERAFLO™ Therapy with VFCC. The authors concluded that the adjunctive use of this therapy may be suitable for wound cleansing in chronic, complex wounds.[22]

Fernandez et al[23] recently reported on their initial experiences in the use of V.A.C. VERAFLO™ Therapy with VFCC in the treatment of five (5) complex pressure ulcer cases. The patients (3 females, 2 males) received debridement when possible, but were limited in undergoing surgery due to the presence of comorbidities or advanced age (range: 50-82 years). This article illustrates an algorithm approach used to determine the appropriate treatment to reach the goals of therapy for each patient. Treatment with V.A.C. VERAFLO™ Therapy with VFCC consisted of instillation of saline or a

hypochlorous solution with a dwell time of 10 minutes, followed by 2-3 hours of -125 mmHg negative pressure. After an average of six (6) days of therapy, all wounds showed a reduction of non-viable tissue and rapid granulation tissue formation. In these cases, V.A.C. VERAFLO™ Therapy with VFCC provided effective and rapid removal of thick exudate and infectious materials and promoted the development of healthy tissue in the wound bed.[23]

1.1.2. Collagenase Ointment

One well-established method of cleansing wounds is to utilize collagenase ointment, which cleanses wounds through the enzymatic cleavage of denatured collagen in non-viable tissue. Collagenase ointment is applied topically once daily and covered with a dressing until cleansing is complete.

A recent systematic review and meta-analysis of RCTs supported the use of collagenase ointment over placebo or alternative therapies for wound healing (eg, wound size reduction or proportion of healed wounds) or wound cleansing (eg, time to clean wound bed or proportion of wounds completely cleansed) of pressure ulcers and DFUs.[24] Individual RCTs have also shown collagenase ointment to be effective in treating chronic ulcers and VLUs, but based on the limited number of RCTs for these wound types, the meta-analysis could not conclude that collagenase was favored.[24] An independent review of RCTs and data from the US Wound Registry showed that collagenase ointment led to better wound healing outcomes (eg, wound closure) in pressure ulcers and VLUs when compared to alternative therapies.[25] Assessment of cost-effectiveness in this review showed collagenase to also be more economical for pressure ulcers and DFUs when compared to other therapies.[25]

1.1.3. Rationale for Studying the Specific Population/Condition

Results from the published studies by Teot et al and Fernandez et al (summarized in Section 1.1.1 above) have provided the evidence needed to pursue this study. It is hypothesized that the mechanisms of action for NPWTi-d will offer a superior method of cleansing the wound and removing exudate, cellular debris, and infectious material. This

could help improve wound healing rates and reduce the risk for complications, thus resulting in clean, healthy, and viable wounds that lead to better outcomes for patients.

Currently, NPWTi-d is only available in the inpatient hospital setting. The most common wounds in the inpatient hospital setting are traumatic wounds, post-surgical wounds, and pressure ulcers/injuries. Of these three types of wounds, pressure ulcers tend to present in a more consistent manner and often would benefit from wound cleansing. However, this study will not restrict the types of wounds that will be assessed.

1.1.4. Rationale for Study Design

In order to have the highest level of evidence, a prospective, multi-center RCT was the study design chosen. Collagenase ointment was selected as the comparator as it is utilized for wound cleansing in various types of wounds (see Section 1.1.2). The proposed study is designed to examine the potential benefits of V.A.C. VERAFLO™ Therapy using VFCC in wounds (eg, chronic, acute, traumatic, or dehisced wounds) and/or ulcers (ie, full-thickness wounds). It is hypothesized that NPWTi-d, in combination with VFCC will use hydromechanical cleansing action to loosen, disrupt and remove non-viable tissue, thereby increasing the wound bed surface area (cm^2) considered to be clean, healthy, and viable. Using a volume of normal saline determined by the treating physician and default device settings for dwell time and NP, the effects of VFCC and V.A.C. VERAFLO™ Therapy will be studied and compared to collagenase ointment. The follow-up time period of 6-9 days is selected due to the series published by Teot et al, where V.A.C. VERAFLO™ Therapy using VFCC was reported to increase the percent surface area of viable tissue (granulation tissue) in the majority of patients after an average of 1-3 dressing changes (3-9 days).[22]

1.1.5. Study Products

The following devices and dressings will be the therapies for the two (2) treatment groups:

- V.A.C.ULTA™ Negative Pressure Wound Therapy System with instillation therapy (ie, V.A.C. VERAFLO™ Therapy) using VFCC and normal saline
- Collagenase ointment with compatible standard dressing

1.1.6. Regulatory Status

The prospective, post-market clinical study described in this protocol will assess the effectiveness and functional performance of the V.A.C.ULTA™ Negative Pressure Wound Therapy System using VFCC and the instillation of saline.

The V.A.C.ULTA™ Negative Pressure Wound Therapy System is a 510(k)–cleared, Class II device (K100657) with the following indication for use: "the V.A.C.ULTA™ Negative Pressure Wound Therapy System is an integrated wound management system that provides negative pressure wound therapy with an instillation option. Negative pressure wound therapy in the absence of instillation is intended to create an environment that promotes wound healing by secondary or tertiary (delayed primary) intention by preparing the wound bed for closure, reducing edema, promoting granulation tissue formation and perfusion, and by removing exudates and infectious material. The instillation option is indicated for patients who would benefit from vacuum-assisted drainage and controlled delivery of topical wound treatment solutions and suspensions over the wound bed. The V.A.C.ULTA™ Negative Pressure Wound Therapy System, with and without instillation, is indicated for patients with chronic, acute, traumatic, sub-acute and dehisced wounds, partial-thickness burns, ulcers (such as diabetic, pressure and venous insufficiency), flaps and grafts". The V.A.C.ULTA™ Therapy Unit is for use with only V.A.C.® Dressings (V.A.C.® GRANUFOAM™ Dressing, V.A.C. GRANUFOAM SILVER™ Dressing, V.A.C. WHITEFOAM™ Dressing, V.A.C. VERAFLO™ Dressing Systems) and disposables. For those Subjects who are randomized into the Treatment arm, V.A.C. VERAFLO™ Therapy will be applied using the V.A.C.ULTA™ Unit and VFCC. VFCC is intended for use with V.A.C. VERAFLO™ Therapy as provided by the V.A.C.ULTA™ Therapy Unit. VFCC was cleared under the V.A.C.ULTA™ Negative Pressure Wound Therapy System 510(k) (K160451). It is recommended for use with open wounds, including wounds with shallow undermining or tunnel areas where the distal aspect is visible.

In this study, various types of wounds will be studied. For this study, the V.A.C.ULTA™ Negative Pressure Wound Therapy System and VFCC will be used in accordance with

their cleared labeling and indications for use and are, therefore, exempt from the investigational device exemptions (IDE) regulation because they meet the conditions for an exempt investigation as provided in 21 CFR 812.2 (c) (2). The system's indications, contraindications, warnings, precautions, and instructions can be found in the V.A.C.ULTA™ Negative Pressure Wound Therapy System Instructions for Use (IFU) document.

1.1.7. V.A.C.ULTA™ Negative Pressure Wound Therapy System

The V.A.C.ULTA™ Negative Pressure Wound Therapy System offers two methods of therapy. The therapy unit delivers both V.A.C.® Therapy (V.A.C.ULTA™ Therapy without instillation) and V.A.C. VERAFLO™ Therapy (V.A.C.ULTA™ with instillation).

The SENSAT.R.A.C.™ Dressing/Technology allows egress of fluid from the wound bed, measures pressure at the wound site, and connects the dressing to the canister tubing.

An exudate canister attaches to the side of the therapy unit and holds the wound and instillation fluid collected from the wound bed.

The V.A.C. VERAFLO™ Therapy option allows for NPWT and instillation of topical wound solutions. The VERAFLO™ Therapy cycle is comprised of an instillation period, a solution dwell or soak period, and an NP period. The user programs the volume of solution to be delivered to the wound bed, the length of time the solution will be allowed to dwell in the wound, and the length of time NP will be applied before the instillation cycle repeats.

V.A.C. VERAFLO™ Therapy using the V.A.C.ULTA™ Negative Pressure Wound Therapy System also includes (Table 1):

- An instillation cassette (V.A.C. VERALINK™ Cassette) connects a solution bag/bottle and the dressing tubing to the therapy unit. The cassette holds and delivers user-provided wound solutions to the wound bed via the automated volumetric pump.
- The V.A.C. VERAT.R.A.C.™ Pad incorporates tubing for fluid input, exudate/fluid removal, as well as pressure sensing at the wound site.

- The V.A.C. VERAFLO CLEANSE CHOICE™ Dressing Kit contains VFCC, which is similar to the V.A.C.® GRANUFOAM™ Dressing but is less hydrophobic for enhanced fluid distribution. VFCC also has improved mechanical properties, including a higher tensile strength. The V.A.C. VERAFLO CLEANSE CHOICE™ Dressing Kit also contains a polyurethane drape (V.A.C.® Advance Drape) with acrylic adhesive, a V.A.C. VERAT.R.A.C.™ Pad, a ruler and 3M™ Cavilon™ No Sting Barrier Film.
- Disposable canisters for the collection of wound exudate are available in three sizes: 300 mL, 500 mL, and 1000 mL. For this study, the 1000-mL canisters will be provided due to instillation.

Table 1: V.A.C.ULTA™ Therapy and V.A.C. VERAFLO CLEANSE CHOICE™ Dressing Kit components.

Name/Description	Picture/Diagram
V.A.C.ULTA™ Therapy Unit	
Exudate Canisters Single-patient use, disposable canister (1000 mL).	
Instillation Cassette (V.A.C. VERALINK™ Cassette) Single patient use, disposable cassette with a spike.	
V.A.C. VERAFLO CLEANSE CHOICE™ Dressing Kit For Subjects in the V.A.C.ULTA™ Therapy with instillation Treatment arm only. Contains: V.A.C. VERAFLO CLEANSE CHOICE™ Dressing; V.A.C.® Advanced Drape; V.A.C. VERAT.R.A.C.™ Pad; Ruler; Cavilon™ No Sting Barrier	

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 (eg, chronic, acute, traumatic, or dehisced wounds) and/or ulcers (ie, full-thickness wounds).

3. STUDY DESIGN

3.1. Design Summary

ACCELERATE Study Schema

Up to 10 Days	*Day 0*	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*	*Day 8*	*Day 9*
SCREENING	**RANDOMIZATION 1:1**	**Collagenase Ointment Treatment**								
		Daily treatment for 6-9 days								
		VFCC and NPWTi-d Treatment								
		Total treatment 6-9 days								
			First change							
					Second change					
							End of Treatment			

This randomized, controlled, prospective multicenter study will enroll Subjects diagnosed with wounds (eg, chronic, acute, traumatic, or dehisced wounds) and/or ulcers (ie, full-thickness wounds) 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. Subjects will receive either VFCC and NPWTi-d (V.A.C. VERAFLO™ Therapy with saline solution) or collagenase ointment to manage their wound over a 6-9-day period. Bedside sharp and/or mechanical debridement procedures will be performed to remove eschar before randomization; however, sharp or mechanical debridement will not be performed after randomization during the treatment phase of the study period (up to 9 days).

For the purposes of this study, we will define and assess viable tissue. Viable tissue will not include the following: non-viable tissue, which can be loose or firmly adherent, hard, soft, dry, or wet. Slough is defined as a type of non-viable fibrinous tissue that consists of fibrin, pus, and proteinaceous material, and could be yellow, white, tan, gray, or green in appearance.

The study will randomize approximately 60 Subjects from approximately 15 sites in a 1:1 ratio to either the VFCC (ie, Treatment) arm or the collagenase ointment (ie, Control) arm after obtaining informed consent, undergoing screening procedures, and meeting all the inclusion criteria and none of the exclusion criteria.

3.1.1. V.A.C. VERAFLO CLEANSE CHOICE™ Dressing

VFCC dressing will be applied to the wound bed and covered with drape material, providing a sealed environment for the application of NPWTi-d for a duration of 6-9 days. The dressing will be applied on Day 0 and changed twice during the treatment period, allowing at least 48 hours between each dressing change. The first dressing change will occur on Day 2-3, and the second dressing change will occur on Day 4-6. The dressing will be removed on Day 6-9 at the treatment endpoint.

3.1.2. Collagenase Ointment

Collagenase ointment will be used as the control for this study as it is a commonly used option for wound cleansing. After application of the ointment, the wound will be covered with a compatible standard-of-care (SOC) dressing for up to nine (9) days. During this treatment period, the ointment can be reapplied once daily (or more frequently if the dressing requires replacement).

3.1.3. Duration of Study Participation

The duration of study participation for each Subject is as follows:

- Screening Period: up to 10 days (Day -10 to Day 0)
- Treatment Period: up to nine (9) days (Day 0 to Day 9)

The maximum participation duration per Subject is up to 19 days.

3.2. Primary Endpoint

The 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.

3.3. Secondary Endpoints

The secondary endpoints are as follows:

- Percent change in total wound volume (cm^3) from baseline to Day 6-9 upon the final dressing removal
- Percent change in total wound area (cm^2) from baseline to Day 6-9 upon the final dressing removal
- Physician assessment of the need for surgical debridement upon completion of study treatment up to Day 6-9

3.4. Exploratory Endpoints

The exploratory endpoints are as follows:

- 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, in the total wound area, and in the total wound volume
- 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 (ie, collagenase ointment applications versus VFCC applications)
- Total time to perform treatment applications and/or dressing changes per Subject

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
- Number of blockage and leak alarms (obtained from the V.A.C.ULTA™ Therapy Unit log)

Additional exploratory endpoints may be added and will be detailed in the statistical analysis plan (SAP).

3.5. Safety Endpoint

The safety endpoint is the Subject incidence of adverse event(s) (AEs).

4. STUDY PROCEDURES AND ASSESSMENTS

4.1. Informed Consent

The Investigator, or designee, will discuss the purpose of this study with potential Subjects or their legally authorized representative if the Subject is unable to provide their own informed consent. Each individual will review the Informed Consent Form (ICF) approved by the local Institutional Review Board (IRB). The ICF must be signed according to IRB requirements before the Subject can undergo any study-related procedures. Informed consent will be obtained under these conditions:

- Subjects or their legally authorized representatives must be made aware of the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected.
- Subjects or their legally authorized representatives must be given the opportunity to ask the Investigator questions and must be provided time to consider participation in the study.
- ICFs will be written in a manner that is non-technical and understandable to the Subject or their legally authorized representative.
- Subjects or their legally authorized representatives will not be led to believe that they are waiving their legal rights to release the Investigator, KCI®, the study site, or any of their agents from liability for negligence.
- Subjects or their legally authorized representatives will be asked to sign and date the ICF indicating their informed consent to participate in the study.
- The Investigator's responsibilities during the ICF process include:

- screening out potential Subjects who may not be able or willing to comply with the study protocol.
- ensuring that Subjects or their legally authorized representatives have signed the ICF prior to undergoing any study-related assessments.
- ensuring that each Subject or their legally authorized representative receives a copy of the signed ICF.

4.2. Inclusion/Exclusion

In order to be considered for randomization, a Subject must meet all eligibility criteria and be assessed no more than 10 days prior to the treatment application. Subjects who do not meet all eligibility criteria will not be eligible for randomization, will discontinue from the study, and will be considered a screen failure. Inclusion and exclusion criteria will be reconfirmed immediately prior to randomization if Visit 1 and Visit 2 are on different dates.

4.2.1. Inclusion Criteria

The Subject:

1. is anticipated to be hospitalized for the duration of treatment (minimum of 6 days).
2. is ≥ 18 years of age.
3. or their legally authorized representative is able to provide informed consent.
4. has been diagnosed with a wound (eg, chronic, acute, traumatic, or dehisced wounds) and/or ulcer (ie, full-thickness wounds) that meets the following criteria:
    a) total surface area measuring ≥ 16 cm^2, including a minimum width of 2 cm (before removal of eschar at the bedside and excluding undermining).
    b) < 20 cm across (edge-to-edge) at any point perpendicular to the wound edges.
5. has, in the opinion of the investigator, no more than 2/3 of the wound bed surface area considered to be clean, healthy, and viable. If eschar is present at baseline, it must be removed by bedside debridement prior to assessing the percentage of

clean, healthy, and viable wound bed.

6. has a negative urine or serum pregnancy test at screening (if female and has potential for pregnancy) and is willing to take precautionary measures to prevent pregnancy during the duration of the study (up to 9 days).

4.2.2. Exclusion Criteria

The Subject:

1. has been diagnosed with malignancy in the wound.
2. has untreated osteomyelitis.
3. has an untreated systemic infection.
4. has active cellulitis in the periwound area.
5. has a known allergy or hypersensitivity to study materials: collagenase ointment, dressing(s), and/or dressing components such as acrylic adhesives or polyurethane.
6. has, in the opinion of the investigator, a clinically significant condition that would impair the Subject's ability to comply with the study procedures.
7. has had radiation directly to the wound area.
8. has been diagnosed with a major vascular deficit limiting arterial inflow to the wound region, as determined by the Investigator's interpretation of the Subject's medical history.
9. has eschar in the wound that cannot be removed by bedside sharp and/or mechanical debridement.
10. is participating in another interventional clinical trial for the duration of the study.
11. has unexplored fistulas in the wound or fistulas in the wound that connect to other body cavities.
12. has a wound with any tunneling present.

13. has inadequate hemostasis at the wound site, as determined by the investigator.

4.3. Premature Study Termination

If the study is terminated prematurely or suspended, study Subjects and the IRB will be informed promptly and provided with the reason(s) for the termination or suspension by KCI® or by the Investigator. If applicable, regulatory authorities and the personal physicians of the Subjects will also be informed.

4.3.1. By Sponsor

KCI® reserves the right to discontinue the clinical study for business or ethical reasons at any time, such as, but not limited to:

- Information regarding the study product causes doubt as to the benefit/risk ratio.
- Changes in medical practice limit utility of the data obtained from the study.

KCI® reserves the right to terminate a study at a site at any time, including but not limited to, any of the following reasons:

- Investigator(s) lack of compliance with the approved study protocol and/or applicable regulatory or IRB guidelines in conducting the study
- Incidence or severity of AEs indicates a potential health hazard or poses an unreasonable risk to the study participants
- Subject enrollment is unsatisfactory
- Fraud or misconduct

4.3.2. By IRB

The IRB may choose to discontinue the study at the site for which they granted approval. If the IRB discontinues the study, the Investigator will report a withdrawal of IRB approval to KCI® within five (5) working days.

4.4. Subject Withdrawal or Termination

4.4.1. Reasons for Withdrawal or Termination

Subjects may withdraw from participation in the study at any time upon request.

The Investigator may choose to terminate the participation of a Subject from the study with or without their consent for any of the following reasons:

- Adverse events
- Noncompliance
- For any reason that may, in the opinion of the Investigator, negatively affect the safety or well-being of the Subject

4.4.2. Handling of Withdrawal or Termination

Every effort should be made to complete wound and AE assessments prior to the Subject withdrawal.

For Subjects who are lost to follow-up, the Investigator will make attempts to collect at least the vital status (eg, whether the Subject is alive) before formally withdrawing the Subject from the study. Prior to considering a Subject lost to follow-up, at least two documented attempts should be made to contact the Subject through all available routes, and a certified letter should be sent to the permanent address on file.

Once the Subject withdraws from the study, no further study evaluations will be performed, and no additional data will be collected. The Investigator may retain and continue to use any data collected before withdrawal. The Subject will not be replaced.

If, for any reason, the Subject is withdrawn by the Investigator from this study, the Investigator will inform the Subject and KCI™.

4.5. Demographics and Subject Characteristics

The following demographic data and Subject characteristics will be collected and documented after the Subject or legally authorized representative signs the informed consent and before treatment application:

- Subject characteristics
- Comorbidities
- Wound history and characteristics

4.6. Medical and Surgical History

As part of screening procedures, the Investigator or a medically licensed sub-investigator, or a practitioner working under the licensure of the Investigator or sub-investigator, will collect a complete medical and surgical history for each Subject. If the screening visit and randomization occur on different days, the medical and surgical history will be updated (if changes have occurred) at the randomization visit prior to treatment application.

4.7. Laboratory Assessment for Pregnancy

Serum or urine assessment for human chorionic gonadotropin (hCG) to determine pregnancy status in female Subjects of child-bearing potential will be conducted during screening. If the Subject's pregnancy test is positive, she will not be eligible for randomization, will discontinue from the study, and will be considered a screen failure.

4.8. Randomization and Subject Numbering

Consented Subjects will be assigned a unique Subject identifier. Study data will be reported according to this unique Subject identifier.

Subjects who satisfy all inclusion criteria and none of the exclusion criteria will be eligible for randomization. Randomization to study treatment will be centralized, electronic, and web-based.

If a screened Subject does not meet all inclusion criteria or meets any exclusion criteria, the Subject will not be randomized and will be considered a screen failure.

4.9. Wound Assessments

Wound assessments will be performed by the Investigator or a medically licensed sub-investigator, or a practitioner working under the licensure of the Investigator or sub-investigator, according to the schedule of visits in order to capture key features of study

wounds (such as odor). A measurement of the study wound will be performed only to determine Subject eligibility.

4.10. Bedside Eschar Debridement

Bedside sharp and/or mechanical debridement procedures will be allowed before randomization to remove eschar. However, sharp or mechanical debridement of the study wound after randomization is not permitted. For those Subjects having bedside sharp and/or mechanical debridement prior to randomization, there will be two wound assessments prior to initiation of treatment.

1) Prior to debridement, the investigator or a medically licensed sub-investigator, or a practitioner working under the licensure of the Investigator or sub-investigator, will measure the wound to confirm that the wound size matches inclusion criteria #4 in Section 4.2.1. In addition, a three-dimensional (3D) image of the wound will be taken prior to debridement.
2) After debridement, the investigator will assess the wound to confirm the wound has no more than 2/3 viable tissue. In addition, a 3D image of the wound will be taken after debridement. This 3D image will be used for the baseline measurement that subsequent images are compared to for any changes in size/tissue composition.

4.11. Initial Application of Study Treatments

4.11.1. V.A.C. VERAFLO CLEANSE CHOICE™ Dressing

For Subjects randomized to the Treatment arm, VFCC will be placed in the wound according to the manufacturer's instructions (safety information and application instructions are provided with the study products). The dressing will be covered with semi-occlusive V.A.C.® Advanced Drape with a quarter-sized hole cut in the drape for the V.A.C. VERAT.R.A.C.™ Pad. The pad should be placed directly over the hole. The normal saline solution will be connected to the system. The pre-programmed therapy unit will then be set to V.A.C. VERAFLO™ Therapy and initiated to deliver a volume determined by the physician along with a 10-minute soak time followed by 3.5 hours of

V.A.C.® Therapy with a pressure of -125 mmHg. During the unit's initial drawdown, the Investigator will evaluate that there is no indication of a system leak using the Seal Check tool. The Investigator or a medically licensed sub-investigator, or a practitioner working under the licensure of the Investigator or sub-investigator, will document therapy unit settings (dwell time, pressure, and cycle time), that the system is operational, and that application of the assigned therapy is successful. Additional V.A.C.® Advanced Drape can be applied to the dressing if needed to assist in mitigating leaks.

The Fill Assist feature on the pump allows the user to monitor initial wound fill by manually starting and stopping instillation to determine correct instill volume after the dressing is applied. The Fill Assist procedure will be performed twice each time a new dressing is placed in the wound. The first time the Fill Assist is performed, the dressing is completely saturated to assist in filling or priming the dressing with a solution and purging the air in the foam. The second Fill Assist procedure is done to determine the appropriate volume to be instilled during therapy. The volume determined from the second Fill Assist procedure will be recorded.

Dressing changes are addressed in Section 4.12. Treatment removal is addressed in Section 4.13.

4.11.2. Collagenase Ointment

For Subjects randomized to the Control arm, the collagenase ointment will be placed in the wound according to the manufacturer's instructions (application instructions are provided with the study products). The approximate therapy amount (such as the total number of tubes used) will be documented. The wound will be covered with a compatible standard dressing, and dressing materials will be documented.

Dressing changes are addressed in Section 4.12. Treatment removal is addressed in Section 4.13.

4.12. Dressing Changes

The date, start time, and end time of each dressing change for both treatment groups (see Sections 4.12.1 and 4.12.2 below) will be documented by the Investigator or a

medically licensed sub-investigator, or a practitioner working under the licensure of the Investigator or sub-investigator.

4.12.1. V.A.C. VERAFLO CLEANSE CHOICE™ Dressing

Dressing changes and treatment application can occur at the bedside. Therapy application instructions are provided with the study products. Dressing change frequency will follow the study schedule of visits (refer to Section 5.1). Dressing changes should not occur more frequently than 48 hours from the previous dressing change unless a replacement is required to maintain therapy. At each dressing change, the Investigator or a medically licensed sub-investigator, or a practitioner working under the licensure of the Investigator or sub-investigator, will document therapy unit settings (dwell time, pressure, and cycle time), that the system is operational, and that application of the assigned therapy is successful for all dressing changes.

4.12.2. Collagenase Ointment

Dressing changes and treatment application can occur at the bedside. Therapy application and dressing changes should be made following the instructions available in the package insert of the product. Dressing changes can occur daily for patients randomized to the collagenase ointment group (or more frequently if dressings become soiled). The approximate therapy amount (such as the total number of tubes used) will be documented for all dressing changes. The wound will be covered with a compatible standard dressing, and dressing materials will be documented for all dressing changes.

4.13. Treatment Removal

4.13.1. V.A.C. VERAFLO CLEANSE CHOICE™ Dressing

Subjects will remain hospitalized and on Study Treatment therapy for two (2) dressing changes (ie, 6 to 9 days). Dressing removal should not occur prior to 48 hours from the previous dressing change unless a replacement is required to maintain therapy. The Investigator may then use their wound treatment of preference to ensure the continuation of wound care. The date and time of dressing removal will be documented.

4.13.2. Collagenase Ointment

Subjects will remain on Study Treatment therapy for six (6) to nine (9) days. The Investigator may then use their wound treatment of preference to ensure the continuation of wound care. The date and time of dressing removal will be documented.

4.14. 3D Imaging

Three-dimensional wound images will be captured for each study visit using a specialized imaging system. Imaging guidelines, equipment, and supplies will be provided to the investigational sites by KCI®.

The 3D images collected from each site will be aggregated into a single database. The aggregated images will be analyzed/measured by the independent assessor. The independent assessor will determine and plot the wound perimeter, the clean, healthy, viable tissue, and other tissue types for each image. The imaging software will be used to calculate wound length, width, surface area, and wound volume. The values of these parameters/assessments will be used for calculations of the primary endpoint as described in section 8.1.1 and the secondary endpoints described in sections 8.1.2.1 and section 8.1.2.2. The 3D wound images should not be used to guide patient treatment.

4.15. Concomitant Medications

Concomitant medications will be collected from the time of randomization through the end of the study. The medication name, start date, end date, and indication will be reported.

Special consideration should be given to report medications that may affect the healing process, such as:

- opioid medications (such as morphine)
- immunosuppressants
- corticosteroids
- non-steroidal anti-inflammatory drugs (NSAID)
- anticoagulant agents (such as heparin)

- all medications with a prophylactic indication
- all medications the Subject is given to treat an AE during the study

4.16. Prohibited Procedures and Treatments

Temporary coverage of the wound for the duration of the study with cell-based skin substitute products such as Apligraf® (Organogenesis), Dermagraft® (Advanced BioHealing), and cadaveric skin is prohibited. For patients in the Control group (collagenase ointment), ointment removal should be performed in a gentle manner and is not intended to be an aggressive mechanical debridement. For Subjects in both groups, no forms of mechanical debridement should be performed for the duration of the study.

4.17. End of Study

The following information will be documented:

- Last day of study participation
- Completion status – Did Subject complete the study (ie, 6-9 days of therapy)?
- Reason for study discontinuation

5. VISIT SCHEDULE AND DESCRIPTION OF STUDY VISITS

5.1. Schedule of Visits

Procedure Description	Visit 1 Screening Day -10 to 0	Visit 2 Randomization Day 0	Visit 3[1] Day 2-3	Visit 4[1] Day 4-6	Visit 5[1] End of Treatment Day 6-9	Unscheduled
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.

5.2. Description of Study Visits

5.2.1. Visit 1/Screening/Days -10 to 0

The following procedures and assessments will be performed and documented in the Subject's medical records/source notes:

- Informed consent
- Inclusion and exclusion criteria
- Demographics and Subject characteristics
- Medical and surgical history
- Laboratory assessment for pregnancy
- Wound assessment, including assessment of wound undermining

5.2.2. Visit 2/Randomization/Day 0

- Inclusion and exclusion criteria confirmation immediately prior to randomization
- Medical and surgical history update, if the Screening Visit and Randomization occur on different days.
- Wound assessment, including assessment of wound undermining (if the patient had eschar sharp and/or mechanical debridement prior to randomization refer to Section 4.10)
- Bedside eschar sharp and/or mechanical debridement (if needed) prior to randomization
- Initial treatment application
- Concomitant medications
- 3D imaging (if the patient had eschar sharp and/or mechanical debridement prior to randomization refer to Section 4.10)
- AE assessment and serious adverse event (SAE) reporting after randomization

5.2.3. Visit 3 and Visit 4/Follow-up Visits/Days 2-3 and Days 4-6

Visits should not occur prior to 48 hours from the previous visit. The following procedures and assessments will be performed and documented in the Subject's medical records/source notes:

- Wound assessment
- Dressing change
- Concomitant medications
- 3D imaging
- AE assessment and serious adverse event (SAE) reporting

5.2.4. Follow-up Visits/Visit 5/End of Treatment/Days 6-9

Visit should not occur prior to 48 hours from the previous visit. The following procedures and assessments will be performed and documented in the Subject's medical records/source notes:

- Wound assessment
- Dressing removal
- 3D imaging
- End of study
- Concomitant medications
- AE assessment and SAE reporting

5.2.5. Unscheduled Visits

Outside of scheduled study visits, if the Subject needs to be assessed by the Investigator or a medically licensed sub-investigator for any reason, the following procedures and assessments will be performed and documented in the Subject's medical records/source notes:

- Wound assessment

- Dressing change
- Dressing removal, if Subject is withdrawn early
- 3D imaging
- End of study, if Subject is withdrawn early
- Concomitant medications
- AE assessment and SAE reporting

6. RISKS ASSOCIATED WITH STUDY PARTICIPATION

Participation in the clinical investigation presents low risks to Subjects. Some risks are generalized and are listed in Tables 2 and 3.

Table 2. Risks Associated With NPWTi-d/VFCC

Risks	Disorders/Conditions
Skin and Subcutaneous Tissue Reaction/Allergy	• Skin rash, irritation, blistering • Pruritus/itching • Skin excoriation/breakdown/stripping • Skin scarring if significant skin irritation were to occur • Maceration • Skin hyper/hypo-pigmentation at and/or around dressing application area • Erythema/redness, edema, inflammation, or swelling at and/or around dressing application area
Mild Pain or Discomfort	• Tenderness/minor ache at and/or around dressing application area • Perspiration associated with wearing dressing • Auditory irritation (due to a mild buzzing sound of negative pressure unit) • Decreased sleep or sleep quality • Paresthesia (numbness, tingling, prickling, creeping sensation) • Pain upon dressing removal
Other	• Bleeding • Localized infection • Autonomic dysreflexia (in Subjects with spinal cord injury) • Retained foreign debris (eg, foam) in the wound • Impairment of mobility/activity (limitation secondary to weight and attachment of therapy unit) • Possible tubing entanglement/trip or slip hazard leading to fracture, tissue damage • Stalled healing/non-progression of healing • Deterioration of the wound • Systemic reaction (due to an allergic reaction to dressing materials)

Table 3: Risks Associated with collagenase ointment

Risks	Disorders/Conditions
Skin and Subcutaneous Tissue Reaction/Allergy	• Collagenase ointment is contraindicated in patients who have shown local or systemic hypersensitivity to collagenase. • A slight transient erythema has been noted occasionally in the surrounding tissue, particularly when collagenase ointment was not confined to the wound. • Pain or burning sensation in the wound
Other	• The optimal pH range of collagenase is six (6) to eight (8). Higher or lower pH conditions will decrease the enzyme's activity and appropriate precautions should be taken. • The enzymatic activity is adversely affected by certain detergents and heavy metal ions such as mercury and silver, which are used in some antiseptics. • Debilitated patients should be closely monitored for systemic bacterial infections because of the theoretical possibility that debriding enzymes may increase the risk of bacteremia.

7. SAFETY AND ADVERSE EVENTS

7.1. Definitions

7.1.1. Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including clinically significant abnormal laboratory findings) in Subjects, users or other persons, whether or not related to the investigational medical device.

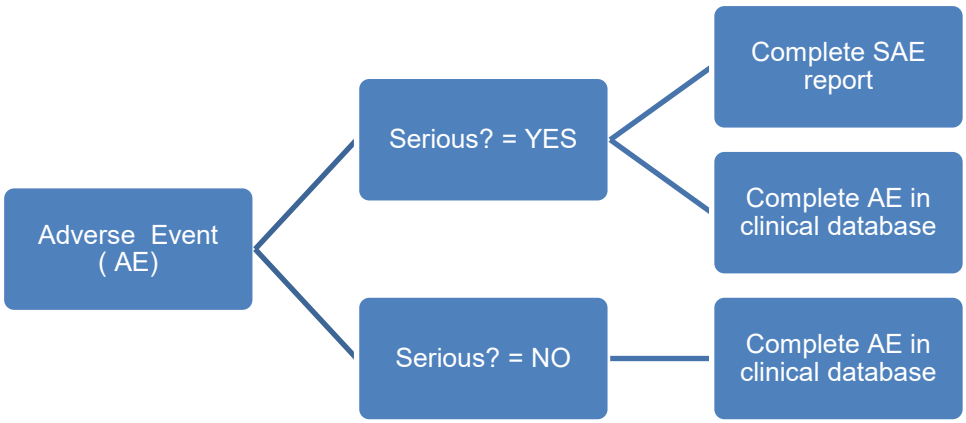
7.1.2. Serious Adverse Event (SAE)

An AE is considered serious if it results in any of the following outcomes:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

- Required intervention to prevent permanent impairment or damage
- Other important medical events may be considered serious when, based upon appropriate medical judgment, they may jeopardize the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.2. Classification



7.2.1. Relationship to Study Treatment

The Investigator will assess the relationship of the AE as:

- **Related** to the study product: any AE for which there is a reasonable possibility that the study product caused the AE. The Sponsor will review all SAEs for expectedness.
- **Not Related** to the study product: when it is determined that there is no relationship between the AE and the use of the study product.

7.2.2. Severity

The Investigator will assign severity as:

- **Mild** – asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated
- **Moderate** – minimal, local, or non-invasive intervention indicated

- **Severe** – medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling

7.3. AE Reporting Procedures

The Investigator is responsible for monitoring the safety of all Subjects enrolled in the study and reporting AEs as described in this protocol.

7.4. AE Collection/Reporting Period

The AE collection/reporting period will begin after the Subject has been randomized. Investigators should assess for AEs at each visit. In addition, study Subjects should be instructed to report any AE that they experience to the Investigator.

All AEs, regardless of perceived relationship to study product, will be reported and recorded on the appropriate case report forms (CRFs) in a timely manner. In addition, the worsening of a medical condition previously reported in the medical history should also be recorded as an AE.

The AE description will include the nature of the experience (AE term), the start date, the end date, the severity of each sign or symptom, the seriousness of the event or experience, relationship to study treatment, the course of action taken, and the outcome of the experience. It will be indicated if the AE caused the Subject to be discontinued from the study.

7.5. SAE Reporting to KCI®

The SAE collection/reporting period will begin after the Subject has been randomized. SAEs will be reported via the KCI® SAE Report Form. This form should be completed by the Investigator, or designee, and submitted (fax or email) to KCI® within 24 hours of the Investigator becoming aware of the event. The KCI® SAE inbox is available for SAE reporting 24 hours per day and is monitored during normal business hours.

7.6. UADE Reporting - Unanticipated Adverse Device Effect (UADE)

A UADE is any SAE on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously

identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of Subjects.

The Sponsor (KCI®) will immediately conduct an evaluation of the received SAEs to determine whether the event meets the UADE definition. If the event is determined to be a UADE, KCI® will report the results of the evaluation to the United States Food & Drug Administration (FDA) and to participating Investigators.

If KCI® determines that the event presents an unreasonable risk to the study Subjects, it will terminate all clinical studies or parts of studies presenting risk as soon as possible.

7.7. Follow-up Period for Ongoing AEs

Treatment-related AEs (serious and non-serious) that are ongoing at the final study visit will be followed up to 30 days to assess resolution or stabilization. All unrelated AEs will be considered closed at the time the Subject completes participation in the study.

8. STATISTICAL CONSIDERATIONS

8.1. Endpoint Definitions for Analysis

8.1.1. Primary Endpoint

The primary endpoint is the 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, which is defined as the difference between the final post-baseline assessment value and baseline value. The percent change in the wound bed surface area (cm^2) considered to be clean, healthy, and viable over time will also be explored and defined in a similar fashion as above utilizing values collected at each visit.

8.1.2. Secondary Endpoints

8.1.2.1. Percent change in total wound volume

This secondary endpoint is the percent change in total wound volume (cm^3) from baseline to Day 6-9 upon the final dressing removal, which is defined as the difference between the final post-baseline assessment value and baseline value, divided by the baseline value and multiplied by 100. The percent change in total wound volume over time will also be explored and defined in a similar fashion as above utilizing values collected at each visit.

8.1.2.2. Percent change in total wound area

This secondary endpoint is the percent change in total wound area (cm^2) from baseline to Day 6-9 upon the final dressing removal, which is defined as the difference between the final post-baseline assessment value and baseline value, divided by the baseline value and multiplied by 100. The percent change in total wound area over time will also be explored and defined in a similar fashion as above utilizing values collected at each visit.

8.1.2.3. Physician assessment of need for debridement

This secondary endpoint is the need for debridement of the wound upon completion of study treatment up to Day 6-9, as assessed by the Investigator. For each Subject, there are three possible outcomes for this endpoint:

- “Yes”, which is assigned if the Subject had a need for wound debridement after the completion of treatment.
- “No”, which is assigned if the Subject had no need for wound debridement after the completion of treatment.
- “Incomplete Treatment”, which is assigned if the Subject did not complete assigned treatment for at least six (6) days.

8.1.3. Safety Endpoints

Treatment-emergent adverse events (TEAE) are those that first appear or worsen after the initial application of the assigned study treatment (ie, V.A.C. VERAFLO™ Therapy using VFCC or collagenase ointment). Adverse events will be coded using the MedDRA dictionary.

8.1.4. Exploratory Endpoints

Additional exploratory endpoints may be added and will be detailed in the SAP. Definitions regarding exploratory endpoints will also be included in the SAP.

8.2. Analysis Sets

The following analysis sets will be used:

- Safety Analysis Set – The Safety Analysis Set will consist of all consented Subjects who received either VFCC and NPWTi-d or collagenase ointment for any length of time. Subjects will be analyzed as treated.
- Intention-to-treat (ITT) Analysis Set – The ITT Set will consist of all randomized Subjects. Subjects will be analyzed as randomized.
- Modified Intent-to-treat (mITT) – The mITT will consist of all randomized Subjects with the following:
  i. met all the inclusion criteria and none of the exclusion criteria,
  ii. 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,
  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.
- Per-Protocol Analysis Set – This set will include Subjects in the mITT who had no disqualifying protocol deviation(s) that would impact the interpretation of the

primary endpoint. The disqualifying protocol deviation(s) for exclusion from this set will be defined and documented in a blinded fashion prior to the final database lock. Subject data will be analyzed in the arm to which they were randomized and treated.

8.3. Planned Analysis and Data Summaries

8.3.1. General Analysis Techniques

In general, continuous variables will be summarized by providing the number of Subjects with available data (n), the mean, median, standard deviation, minimum, and maximum values. For categorical variables, the number and percentage of Subjects that are in each category will be provided. Unless otherwise specified, the denominator for percentages will be all relevant Subjects in a specified analysis set, including those for whom data are not available, ie, “not reported” or “not available” – those data will generally be considered a separate category and included in the displays of data, with the denominator for percentages including these Subjects. Subjects will be summarized by treatment group and overall.

8.3.2. Subject Disposition

Summaries of disposition will be tabulated by treatment group. The number and percentage of Subjects in the specified analysis set will be described, as will the number and percentage of Subjects who:

- provided informed consent
- failed screening, and the reason for screen failure
- were randomized and treated
- discontinued early from the study for any reason, along with the reason for discontinuation (if the reason is an AE, the system organ class and preferred term)
- completed the study as planned

Subject disposition also will be described in a flowchart (CONSORT diagram).

8.3.3. Demographic and Baseline Characteristics

Demographic characteristics (eg, age, sex, race, and ethnicity), baseline characteristics, and other disease characteristics will be summarized per the general techniques in Section 8.3.1. Subjects in the mITT, ITT, and/or Per-Protocol Analysis Sets will be summarized by treatment arm and overall.

8.3.4. Analysis of Primary Endpoint

The primary endpoint will be calculated per the definition in Section 8.1.1. Based on the mITT analysis set, the primary endpoint will be summarized by treatment group and overall.

The null and alternative hypotheses for the primary endpoint are:

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

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

Assessments will be taken at multiple visits for each Subject during the study. The primary endpoint will be analyzed using a repeated measures analysis of covariance model (ANCOVA) with treatment arm, visit, wound undermining measurement, clinical site, and treatment by visit (Note: if clinical site or treatment by visit are not statistically significant, then the non-significant term(s) will be removed from the model and the updated model will be re-run). The analysis will be based on the mITT analysis set.

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

- repeat the analysis above on the ITT and Per-Protocol analysis sets
- a two-sample t-test or a Wilcoxon Rank-Sum test without adjusting for wound undermining
- analyses comparing the treatment groups considering covariates (eg, age, body mass index [BMI], race/ethnicity, sex, wound undermining, and co-morbidities) and subsets of the data

8.3.5. Analysis of Secondary Endpoints

8.3.5.1. Percent change in total wound volume

This secondary endpoint will be calculated per the definition in Section 8.1.2.1 and will be analyzed in a similar fashion as the primary endpoint described in Section 8.3.4.

8.3.5.2. Percent change in total wound care

This secondary endpoint will be calculated per the definition in Section 8.1.2.2 and will be analyzed in a similar fashion as the primary endpoint described in Section 8.3.4.

8.3.5.3. Physician assessment of the need for debridement

This secondary endpoint will be calculated per the definition in Section 8.1.2.3. Based on the mITT analysis set, the proportion of Subjects with each possible result will be summarized by treatment group and overall.

The comparative analysis of this secondary endpoint will only consider Subjects in the mITT set. Treatment groups (VFCC and NPWTi-d vs collagenase ointment) will be compared with a Chi-square or Fisher's exact test, as appropriate.

If appropriate, supportive/exploratory analyses of this secondary endpoint may include:

- repeat the analysis above on the ITT and Per-Protocol analysis sets
- analyses comparing the treatment groups considering covariates (eg, 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.

8.3.6. Exploratory Analyses

In general, all exploratory, supplementary or sensitivity analyses/endpoints will be performed using methods outlined in Section 8.3.1. Because the analyses are exploratory, no adjustment will be made for multiple comparisons. Additional exploratory endpoints and specifics regarding analyses will be specified in the SAP.

8.3.7. Analysis of Safety Endpoint

All safety results will be presented based on the Safety Analysis Set. All TEAEs will be summarized by treatment arm. Subject incidence of TEAEs will be summarized by treatment arm and by MedDRA system organ class and preferred term. For each coded medical term, the proportion of Subjects who experience at least one treatment-emergent:

- adverse event(s);
- adverse event(s) related to treatment
- serious adverse event(s);
- serious adverse event(s) related to treatment
- adverse event(s) by severity (mild, moderate, severe);
- adverse event(s) leading to treatment/study discontinuation, or
- serious adverse event(s) leading to treatment/study discontinuation will be reported.

A listing of death(s), Subjects who died of any cause during the study, will be presented.

8.4. Additional Statistical Details

8.4.1. Sample Size Determination

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 common standard deviation of 22%, 23 evaluable Subjects per group will provide approximately 80% power to detect a statistically significant difference using the Wilcoxon Rank-Sum test (n Query Advisor® 7.0).

It is possible that some wounds assessed by the independent assessor will not meet the baseline requirement of no more than 2/3 area of a clean, healthy, viable wound bed as

measured by a 3D camera, even though the investigator assessed the wound at ≤ 2/3 area of clean, healthy, viable wound bed. 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 (ie, 30 Subjects per arm).

8.4.2. 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.

8.5. Open-Label Study Reporting Results

All precaution will be taken to avoid operational bias introduced by statistical analysis. While the study is ongoing, summary statistics by treatment arms across all sites may be limited to a small analytical group not involved in the daily operations of the study. Treatment arms may be masked in the summary reports or outputs (tables, listings, and figures) if needed. The limited analysis results will be shared with Investigators and IRBs as necessary to conduct the study.

Upon study completion, the full results will be shared with all investigators and clinical sites.

8.6. Interim Analysis

A nonbinding, 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-calculation.

The primary endpoint will be analyzed as outlined in Section 8.3.4. If the resulting p-value for the primary analysis is less than α=0.006 as determined utilizing the O'Brien-Fleming α-spending function (O'Brien 1979),[26] the null hypothesis will be rejected, and the study may be stopped for efficacy.

If the null hypothesis could not be rejected, conditional power will be calculated to assess for futility and/or sample size adjustment. If the conditional power is lower than the pre-specified boundary in the interim SAP, the trial may be stopped for futility. If the conditional power is above the futility boundary, the conditional power will be evaluated utilizing methods described in Chen et al (Chen 2004) to determine if a sample size increase is required.[27]

The final analysis will be conducted at α=0.048 to maintain the overall type I error rate at α=0.05 as determined by the O'Brien-Fleming spending function. Details of the interim analysis will be described in the interim SAP before the interim analysis is conducted.

8.7. Statistical Analysis Plan and Changes in Analyses

A separate SAP containing full details of the statistical analysis and execution will be finalized prior to the study database lock and the final analysis. Any changes from planned analyses in the study protocol or from the SAP will be noted in the Clinical Study Report (CSR).

9. HANDLING OF STUDY PRODUCTS

Study product receipt, use, dispensation, destruction, and return records will be maintained throughout the study.

Upon receipt of product, the Investigator, or designee, will inventory the shipment and immediately notify KCI® if study product or other study supplies are missing. The monitor

will verify that study product documentation is maintained appropriately during monitoring visits.

At the completion of the study, there will be a final reconciliation of study product shipped, used, and unused. Any unused study product and associated supplies will be returned to KCI®.

10. DATA HANDLING AND RECORD KEEPING

10.1. Investigator/Study Site Training

The Investigator and site staff will be trained on the protocol, the study products, and any specialized procedures prior to enrolling Subjects into the study. KCI® will provide support to site staff for any questions or concerns related to study products and procedures. KCI® will not have an influence on Subject medical care.

10.2. Electronic Case Report Form (eCRF) and Source Documents

Source documents include all information in original records, certified copies of original records, observations, or other activities necessary for the reconstruction and evaluation of the study. All source documents should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of the data.

Data from source documents of each Subject will be entered into the Subject's electronic Case Report Form (eCRF). Guidance for eCRF completion will be provided and reviewed with the site staff prior to receiving study product.

10.3. Monitoring of Study Data

The data will be entered into the clinical study database by Investigative Site staff and verified for accuracy by a KCI® representative. The Investigator will allow access to his/her clinical study records for periodic on-site monitoring visits by a designated KCI® representative, with the understanding that the representative is bound by professional secrecy and will not disclose a Subject's personal identity or personal medical information. The representative will review eCRFs for completeness during on-site

monitoring visits, and after the eCRFs are submitted; any discrepancies will be resolved with the Investigator or designee, as appropriate.

10.4. Data Handling

KCI® is responsible for compilation and verification of the clinical study data, retention of the clinical study database, performance of statistical analysis, and preparation of the CSR.

10.5. Records Retention

The study site will maintain all study documentation and institute measures to prevent the accidental or premature destruction of any data and/or documents related to the study.

After formal discontinuation or completion of the study, the Investigator will retain all clinical study documentation for a minimum of two (2) years from the date the investigation is terminated or completed or in accordance with the regulations in effect for the jurisdiction where the site is located. The Investigator will contact KCI® prior to the destruction of any study records.

11. ADMINISTRATIVE REQUIREMENTS

11.1. Good Clinical Practice (GCP)

This study is to be conducted according to the US and international standards of good clinical practice such as the International Conference on Harmonization guidelines, applicable government regulations (eg, FDA CFR Title 21 part 812), and institutional research policies and procedures.

11.2. Ethical Considerations

This study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. Approving IRBs will be provided all relevant study documentation in order to safeguard the rights, safety, and well-being of Subjects as mandated. Participating Investigators will obtain IRB approval of the study prior to initiation at their sites. The protocol, IFUs, informed consent, written information given to Subjects, safety

updates, and any revisions to these documents will be provided to the IRB by the Investigator.

11.3. Subject Informed Consent

Written informed consent will be obtained from a potential Subject or their legally authorized representative if the Subject is unable to provide their own informed consent after the study has been fully explained and prior to the conduct of any study-related procedures. Obtaining informed consent is a process that must be documented in compliance with GCP, IRB, and other applicable regulatory requirements (21 CFR part 50). The Investigator is responsible for continuing an open conversation with the Subject or their legally authorized representative in regard to their continued participation in the study. KCI® will conduct periodic monitoring to ensure informed consent is obtained for each Subject prior to any study procedures.

11.4. Confidentiality

Information collected about Subjects during the study will be kept confidential and managed according to the requirements of the IRB and Health Insurance Portability and Accountability Act of 1996 (HIPAA).

In the event that a Subject revokes an authorization to collect or use Personal Health Information (PHI), the Investigator retains the ability to use all information collected prior to the revocation of Subject authorization.

11.5. Clinicaltrials.gov Registration

A description of this study will be available on http://www.ClinicalTrials.gov as required by U.S. law. This website will not include information that identifies Subjects. At most, the website will include a summary of the results of the study and will be available for public review at any time.

11.6. Auditing and Inspecting

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance and quality assurance offices.

The Investigator will permit study-related monitoring, audits, and inspections of all study-related documents (eg, source documents, regulatory documents, data collection instruments, study data) by the IRB/IEC, KCI® or its designee, and government regulatory bodies.

12. REFERENCES

(1) Konig M, Vanscheidt W, Augustin M, Kapp H. Enzymatic versus autolytic debridement of chronic leg ulcers: a prospective randomised trial. *J Wound Care* 2005;14:320-323.

(2) Sen CK, Gordillo GM, Roy S et al. Human skin wounds: a major and snowballing threat to public health and the economy. *Wound Repair Regen* 2009;17:763-771.

(3) Fife CE, Carter MJ, Walker D, Thomson B. Wound care outcomes and associated cost among patients treated in US outpatient wound centers: Data from the US Wound Registry. *Wounds* 2012;24:10-17.

(4) Landen NX, Li D, Stahle M. Transition from inflammation to proliferation: a critical step during wound healing. *Cell Mol Life Sci* 2016.

(5) MacLeod AS, Mansbridge JN. The Innate Immune System in Acute and Chronic Wounds. *Adv Wound Care* 2016;5:65-78.

(6) Cutting KF, Vowden P, Wiegand C. Wound inflammation and the role of a multifunctional polymeric dressing. *Wounds International* 2015;6:41-42, 44.

(7) Morykwas MJ, Argenta LC. Use of negative pressure to prevent progression of partial thickness burns [abstract]Morykwas MJ, Argenta LC. *Presented at the 26th Annual Meeting of the American Association of Plastic Surgeons, 1994 Joint Meeting of European Tissue Repair Society and the Wound Healing Society in Amsterdam Netherlands, 1993* 1993;

(8) Fleischmann W, Russ M, Westhauser A, Stampehl M. [Vacuum-sealing-technique used as drug release system for topical treatment of wound infections]. *Unfallchirurg* 1998;101:649-654.

(9) Allen D, LaBarbera LA, Bondre IL et al. Comparison of tissue damage, cleansing and cross-contamination potential during wound cleansing via two methods: lavage and negative pressure wound therapy with instillation. *Int Wound J* 2014;11:198-209.

(10) Yang C, Goss SG, Alcantara S, Schultz G, Lantis Ii JC. Effect of Negative Pressure Wound Therapy With Instillation on Bioburden in Chronically Infected Wounds. *Wounds* 2017;29:240-246.

(11) Brinkert D, Ali M, Naud M, Maire N, Trial C, Teot L. Negative pressure wound therapy with saline instillation: 131 patient case series. *Int Wound J* 2013;10:56-60.

(12) Ciancio F, Parisi D, Portincasa A, Innocenti A. Discussion: A New Method of Salvaging Breast Reconstruction After Breast Implant Using Negative-Pressure Wound Therapy and Instillation. *Aesthetic Plast Surg* 2017;41:466-467.

(13) Gabriel A, Kahn K, Karmy-Jones R. Use of negative pressure wound therapy with automated, volumetric instillation for the treatment of extremity and trunk wounds: clinical outcomes and potential cost-effectiveness. *Eplasty* 2014;14:e41.

(14) Goss SG, Schwartz JA, Facchin F, Avdagic E, Gendics C, Lantis JC, II. Negative Pressure Wound Therapy with Instillation (NPWTi) Better Reduces Postdebridement Bioburden in Chronically Infected Lower Extremity Wounds than NPWT Alone. *Journal of the American College of Clinical Wound Specialists* 2014;4:74-80.

(15) Kim PJ, Attinger CE, Steinberg JS et al. The impact of negative-pressure wound therapy with instillation compared with standard negative-pressure wound therapy: a retrospective, historical, cohort, controlled study. *Plast Reconstr Surg* 2014;133:709-716.

(16) Kim PJ, Attinger CE, Oliver N et al. Comparison of Outcomes for Normal Saline and an Antiseptic Solution for Negative-Pressure Wound Therapy with Instillation. *Plast Reconstr Surg* 2015;136:657e-664e.

(17) Gupta S, Gabriel A, Lantis J, Teot L. Clinical recommendations and practical guide for negative pressure wound therapy with instillation. *Int Wound J* 2016;13:159-174.

(18) Kim PJ, Attinger CE, Steinberg JS et al. Negative-Pressure Wound Therapy with Instillation: International Consensus Guidelines. *Plast Reconstr Surg* 2013;132:1569-1579.

(19) Kim PJ, Attinger CE, Crist BD et al. Negative pressure wound therapy with instillation: review of evidence and recommendations. *Wounds* 2015;27:S2-S19.

(20) McKanna M, Geraci J, Hall K et al. Clinician panel recommendations for use of negative pressure wound therapy with instillation. *Ostomy Wound Manage* 2016;3-14.

(21) Powers K, Attinger C, Evans K, Kim P, Steinberg J. Early Experience with Negative Pressure Wound Therapy with Instillation in Acutely Infected Wounds: Preliminary Data [abstract]Powers K, Attinger C, Evans K, Kim P, Steinberg J. *Presented at Diabetic Limb Salvage 2012, October 11-13, 2012, Washington, DC* 2012;

(22) Teot L, Boissiere F, Fluieraru S. Novel foam dressing using negative pressure wound therapy with instillation to remove thick exudate. *Int Wound J* 2017;14:842-848.

(23) Fernandez L, Ellman C, Jackson P. Initial experience using a novel reticulated open cell foam dressing with through holes during negative pressure wound therapy with instillation for management of pressure ulcers. *Journal of Trauma and Treatment* 2017;6:410.

(24) Patry J, Blanchette V. Enzymatic debridement with collagenase in wounds and ulcers: a systematic review and meta-analysis. *Int Wound J* 2017;14:1055-1065.

(25) Waycaster C, Carter MJ, Gilligan AM, Mearns ES, Fife CE, Milne CT. Comparative cost and clinical effectiveness of clostridial collagenase ointment for chronic dermal ulcers. *Journal of Comparative Effectiveness Research* 2017.

(26) O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-556.

(27) Chen YH, DeMets DL, Lan KK. Increasing the sample size when the unblinded interim result is promising. *Stat Med* 2004;23:1023-1038.