# A Randomized Controlled Trial of Enzymatic Debridement of Pressure Ulcers with Clostridial Collagenase Ointment (SANTYL®) or Hydrogel (SoloSite®)

| | |
|---|---|
| Protocol Number: | 017-101-09-036 |
| Sponsor Name & Address: | Smith & Nephew, Inc<br>3909 Hulen Street<br>Fort Worth, Texas 76107 |
| Test and Control Article(s): | Collagenase SANTYL® Ointment<br>Hydrogel (SoloSite®) |
| Protocol Version | <1, Original Issue, 27-Jan-2016><br>**<2, Incorporating Amendment 1, 05-May-2016>** |

# 1. SIGNATURES

## 1.1 INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "A Randomized Controlled Trial of Enzymatic Debridement of Pressure Ulcers with Clostridial Collagenase Ointment (SANTYL®) or Hydrogel (SoloSite®)", Version 2, dated 05-May--2016, and agree to abide by all provisions set forth therein.

I agree to comply with the Investigator Obligations stipulated in Section 13 of the protocol.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the described clinical investigation without the prior written consent of Smith & Nephew, Inc.

Signature

Name of Principal Investigator (print)

Date

## 1.2 SPONSOR APPROVAL

Herbert B. Slade, MD, FAAAAI — Date: 12 May 16
Chief Scientific & Medical Officer, Advanced Wound Management

Jaime E. Dickerson, PhD — Date: 12 MAY 2016
VP, Global Medical & Clinical Affairs and Medical Monitor

Bobbi Drais, MS, RAC — Date
VP, Regulatory Affairs, Advanced Wound Management

Alan Rossington, MEng, MSc — Date
Director, Biostatistics and Data Management, Global Medical & Clinical Affairs

## 1.3 SPONSOR REVIEW

Paul Martin — Date: 17 MAY 16
Sr. Manager, Quality Assurance

## 1.2 SPONSOR APPROVAL

Herbert B. Slade, MD, FAAAAI — Date: 12 May 16

Chief Scientific & Medical Officer, Advanced Wound Management

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Paul Martin — Date

Sr. Manager, Quality Assurance

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| Bobbi Drais 16 MAY 2016<br>Bobbi Drais, MS, RAC Date<br>VP, Regulatory Affairs, Advanced Wound Management | Alan Rossington, MEng, MSc Date<br>Director, Biostatistics and Data Management, Global Medical & Clinical Affairs |

## 1.3 SPONSOR REVIEW

Paul Martin Date
Sr. Manager, Quality Assurance

## 1.2 Sponsor Approval

Herbert B. Slade MD 10 May 16 — 12 MAY 2016

| | | | |
|---|---|---|---|
| Herbert B. Slade, MD, FAAAAI | Date | Jaime E. Dickerson, PhD | Date |
| Chief Scientific & Medical Officer, Advanced Wound Management | | VP, Global Medical & Clinical Affairs and Medical Monitor | |
| Bobbi Drais, MS, RAC | Date | Alan Rossington, MEng, MSc | Date |
| VP, Regulatory Affairs, Advanced Wound Management | | Director, Biostatistics and Data Management, Global Medical & Clinical Affairs | |

17 May 2016.

## 1.3 Sponsor Review

| | |
|---|---|
| Paul Martin | Date |
| Sr. Manager, Quality Assurance | |

## 2. SYNOPSIS

| | |
|---|---|
| Study Phase: | 4 |
| Financial Disclosure Information for U.S. FDA Submission to be Obtained? | ☐ Yes ☒ No |
| Test Article(s) / Products: | Collagenase SANTYL® Ointment<br>Hydrogel (SoloSite®) |
| Study Dosage / Usage: | Daily application directly to the ulcer bed, approximately 2-5 mm thick |
| Active Ingredients: | Collagenase enzymes derived from *C. histolyticum*, 250 collagenase units per gram of white petrolatum USP |
| Route of Administration: | Topical |
| Objective(s): | The primary objective of this study is to compare Collagenase SANTYL® Ointment versus hydrogel in the proportion of ulcers achieving complete debridement following 6 weeks of treatment.<br>The secondary objectives are to compare, between groups,<br>• The time in days to complete debridement;<br>• The percentage reduction in the percentage of non-viable tissue over the 6-week treatment period and at each assessment visit;<br>• The percentage reduction in wound area over the 6-week treatment period and at each assessment visit;<br>• Change in wound status as measured by the Pressure Ulcer Scale for Healing (PUSH) and Wound Bed Score (WBS) tools following 6 weeks of treatment.<br>The exploratory objective of this study is to determine if there is a difference in resource utilization between the two treatment groups. |
| Study Population: | Adults aged 18 years and older with a pressure ulcer between 1.0 and 64.0 $cm^2$ in area (inclusive) and at least 85% necrotic, non-viable tissue |

| | | | | |
|---|---|---|---|---|
| Structure: | [X] | Parallel Group | Duration of Treatment: | Up to 6 weeks |
| | | | Duration of Assessment: | Up to 8 weeks |
| | [ ] | Crossover | Number of Treatments: | N/A |
| | | | Number of Sequences: | N/A |
| | | | Number of Periods: | N/A |
| | | | Duration of Periods: | N/A |
| | | | Washout Between Periods: | N/A |
| | [ ] | Other | N/A | |
| | | | Duration of Treatment: | N/A |

| | | | |
|---|---|---|---|
| Multi-Center: | [ ] | Yes | Number of Centers: 1 |
| | [X] | No | |

| | | |
|---|---|---|
| Blinding: | [ ] | None |
| | [X] | Observer-Blind |
| | [ ] | Subject-Blind |
| | [ ] | Double-Blind |

| | | | |
|---|---|---|---|
| Randomization: | [X] | Yes | Group Assignment Ratio: 1:1 |
| | [ ] | No | |

| | | | |
|---|---|---|---|
| Concurrent Control: | [ ] | No Treatment | |
| | [X] | Standard Care | Specify: Hydrogel (SoloSite®) |
| | [ ] | Placebo | Specify: N/A |
| | [ ] | Active | Specify: N/A |
| | [ ] | Other | Specify: N/A |

Estimated Total Sample Size: Approximately 32 subjects will be randomized to ensure at least 26 complete the study

| | | |
|---|---|---|
| Statistical Rationale Provided: | [X] | Yes |
| | [ ] | No |

Variable(s): PRIMARY: Proportion of ulcers with complete debridement

| | |
|---|---|
| SECONDARY: | Time in days to complete debridement<br>Percentage reduction in non-viable tissue<br>Percentage reduction in ulcer area<br>PUSH score<br>WBS score |
| EXPLORATORY: | N/A |
| SAFETY: | Adverse events |
| PK: | N/A |
| | Refer to Section 10 for Statistical Design. |

Adverse Events: [X] Both volunteered and elicited
[ ] Other: N/A

## 3. TABLE OF CONTENTS

## 3.1 TABLE OF TABLES



## 3.2 TABLE OF FIGURES

## 3.3 List of Abbreviations and Definitions of Terms

| Abbreviation | Definition |
|---|---|
| ABI | Ankle Brachial Index |
| ADR | Adverse Drug Reactions |
| AE | Adverse Event(s) |
| CRF | Case Report Form |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HbA1c | Hemoglobin A1c |
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat |
| LOCF | Last Observation Carried Forward |
| N or n | Sample Size |
| NA or N/A | Not Applicable |
| PP | Per Protocol |
| PUSH | Pressure Ulcer Scale for Healing |
| SAE | Serious Adverse Event(s) |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis Software, SAS® Institute, Cary, NC |
| UPT | Urine Pregnancy Test |
| WBS | Wound Bed Score |

# 4. INTRODUCTION

## 4.1 BACKGROUND

Pressure ulcers are localized injuries to the skin and underlying tissues, usually over a bony prominence, as a result of pressure and/or shear (1). The proximate causes may be tissue ischemia resulting from restriction of blood supply through the capillaries or alternatively cellular distortion and damage. The effect of stress and strain on deeper tissues must also be considered (2). Factors that may contribute to the breakdown of tissue include moisture, friction, and irritants as well as intrinsic factors such as age, tissue perfusion, nutrition, smoking, diabetes, and steroid treatment, to name just a few (3). Aside from the impact pressure ulcers have on patient health and quality of life, pressure ulcers represent a significant financial cost, not only for institutions and facilities, but also to patients and their families.

Treatment of pressure ulcers is generally aimed at elimination of the cause, i.e., pressure redistribution via repositioning strategies and support structures in conjunction with wound bed preparation consisting of infection control, moisture balance, and debridement (3). Debridement is of particular importance in wound bed preparation as the presence of necrotic tissue in the wound bed represents a burden of senescent cells, dysfunctional extracellular matrix, along with an inflamed proteolytic environment that must be overcome in order for healing to proceed (4,5). Debridement can be accomplished by various means including sharp surgical methods, mechanical (e.g., wet-to-dry gauze), biological (maggots), and enzymatic (collagenase). While sharp surgical debridement is generally acknowledged to be the "gold standard" (6), other methodologies are necessarily employed in situations where there may be a risk of excessive bleeding or where the use of surgical instruments is outside the scope of practice of the wound care practitioners at, for example, a long-term care facility (6,7).

Enzymatic debridement with collagenase has previously been shown to be an effective means of wound bed preparation when used without accompanying sharp debridement for pressure ulcers (7), and for diabetic foot ulcers (8), although additional benefits may be possible if used in

conjunction with sharp debridement (9). In the long-term care setting, debridement with collagenase resulted in more patients achieving complete debridement, more rapidly than when a hydrogel was used (7). The goal of the present study is to confirm the results of this earlier trial, demonstrating superior debridement outcomes for pressure ulcers of patients in long-term care as compared to ulcers managed with a hydrogel.

A summary of known and potential risks and benefits to humans associated with the use of collagenase SANTYL® ointment can be found in the Investigator's Brochure.

### 4.2 RATIONALE

Reproducibility is a cornerstone of the scientific method. Indeed, Popper has stated that, "non-reproducible single occurrences are of no significance to science" (10). It is commonly accepted that reproducibility is a necessary condition for the establishment of a scientific fact. According to the National Institute of Standards and Technology, replication of an experiment should include the following elements: the same experimental tools, the same observer, the same measuring instrument used under the same conditions, the same location, repetition over a short period of time, and the same objectives (11). From a practical standpoint it is not generally possible to meet all of these criteria, nevertheless, the design of the present study seeks to replicate as closely as possible the design of a prior study comparing enzymatic debridement with collagenase to passive treatment with a hydrogel. To this end, the study design (i.e., size, number of visits, parallel group, choice of comparator), setting (long-term care facility), inclusion/exclusion criteria, treatment regimen (daily application, no concomitant sharp debridement) endpoints, and objectives are identical to the previous study. The measurement tools are also the same including the PUSH (12) and WBS (13) scales. One of the two observers assessing the ulcer photographs will be the same, although one will be different. However a mechanism to establish consensus in cases of disagreement should mitigate the risk of subjective bias having an important influence on the results. Finally, the objectives of this study exactly match those of the previous trial.

## 5. OBJECTIVE

The primary objective of this study is to compare Collagenase SANTYL® Ointment versus hydrogel in the proportion of ulcers achieving complete debridement following 6 weeks of treatment.

The secondary objectives are to compare, between groups, the time in days to complete debridement; the percentage reduction in the percentage of non-viable tissue over the 6-week treatment period and at each assessment visit; the percentage reduction in wound area over the 6-week treatment period and at each assessment visit; change in wound status as measured by the PUSH and WBS tools following 6 weeks of treatment.

The exploratory objective of this study is to determine if there is a difference in resource utilization between the two treatment groups.

## 6. TEST ARTICLES

### 6.1 IDENTIFICATION

| | |
|---|---|
| Test Article: | Collagenase SANTYL® Ointment – Collagenase enzymes derived from *C. histolyticum*, 250 collagenase units per gram of white petrolatum USP. |
| Control Article: | SoloSite® hydrogel |

### 6.2 USAGE

Following normal saline irrigation, SANTYL or SoloSite (depending on treatment assignment) will be applied once daily. SANTYL will be applied directly to the entire wound bed, approximately 2 mm thick (thickness of a nickel). SoloSite will be applied directly to the entire wound bed, approximately 5 mm thick. For both treatment groups, the wound will then be covered with a semi-occlusive dressing (e.g., COVRSITE™). Should the dressing integrity be compromised due to fecal or urinary incontinence, or through inadvertent removal, additional application and dressing should be applied.

### 6.3 PACKAGING AND LABELING

Packaging and labeling will be prepared to meet regulatory requirements.

The labels on the test article contain the following information:

Study number: 017-101-09-036

Tube number

Subject Number

Place for the Subject Initials

"MUST be Stored at Room Temperature"

Exclusively for Clinical Evaluation Only

Smith & Nephew, Inc., Fort Worth, TX

### 6.4 TEST ARTICLE ACCOUNTABILITY PROCEDURES

When a delivery of test article is received at the investigational site, the Investigator, or a member of his/her staff specifically authorized and delegated by the Investigator, will check for accurate delivery and acknowledge receipt by signing and dating the required documentation and returning it as instructed. A copy of this documentation will be retained for the Investigator file.

The test article will be stored at room temperature and a temperature log will be maintained by the site.

The receipt, dispensing, and return of test article will be carefully recorded on appropriate accountability forms available for verification by the Sponsor or its designated representative at each monitoring visit. The nursing staff is to be instructed to retain all used and unused test article tubes. Used test article must not be discarded or destroyed by site staff but will be retained for study monitor verification.

# 7. SUBJECTS

## 7.1 SUBJECT POPULATION

The study population will consist of approximately 32 adult subjects with a pressure ulcer between 1.0 and 64.0 $cm^2$ in area (inclusive), and with at least 85% of the surface covered by necrotic, non-viable tissue.

## 7.2 INCLUSION CRITERIA

Subjects will be considered qualified for enrollment if they meet the following criteria:

1. Provide written informed consent, which will consist of reading, signing, and dating the informed consent document after the Investigator, sub-Investigator or other designated study staff member has explained the study procedures, risks, and contact information.
2. Eighteen years of age or older, of either sex, and of any race.

3. Willing to comply with protocol instructions, including allowing all study assessments.
4. Subject is in-patient in a long-term care facility.
5. A pressure ulcer present with a surface area $\geq 1.0$ cm$^2$ and $\leq 64.0$ cm$^2$ confirmed using the ImageIQ EDCIQ mobile imaging system. Only one qualifying ulcer per subject will be selected for the study (selection based on greatest clinical need, as assessed by the Investigator).
6. The target ulcer must present with ≥85% necrotic, nonviable tissue as assessed by at least one independent image reviewer.
7. The target ulcer has not been previously treated with hydrogel (SoloSite®) or with SANTYL. Prior ulcers at or near the same location may have been treated with these products.
8. No current infections requiring treatment with antibiotics (antibiotic use is permitted for the purpose of urinary tract infection ***prophylaxis***, but this must be explicitly stated in the subject's chart).
9. Acceptable state of health and nutrition with pre-albumin levels of ≥ 10 mg/dL (0.10 g/L), per the Screening local lab report. This is not required if a pre-albumin test within range has been conducted within the last 30 days.
10. A hemoglobin A1c < 7.9% per the Screening local lab report. This is not required if a hemoglobin A1c test within range has been conducted within the last 30 days.

11. Have adequate pressure redistribution to the affected area or off-loading if the ulcer is on a lower extremity.
12. No known allergies or sensitivities to either test article or the dressings.
13. Women of child-bearing potential (those who are not premenarchal, not surgically sterilized [hysterectomy or bilateral oophorectomy], or not post-menopausal), may participate in the study if they meet the following condition:
    - A negative urine pregnancy test at screening

### 7.3 EXCLUSION CRITERIA

Any one (1) of the following criteria will disqualify a potential Subject from participation in the study. The Medical Monitor may also declare any subject ineligible for a valid medical reason.

1. Undergoing therapy with another investigational agent within thirty (30) days of Study Visit 1, or planned participation overlapping with this study.
2. Current oral steroid treatment with a daily dose exceeding 5 mg.
3. Inability to comply with off-loading.
4. If the ulcer is on a lower extremity, inadequate arterial blood flow to the affected limb as evidenced by an ankle brachial index (ABI) <0.85.
5. Presence of callus requiring surgical debridement within 3 days of Study Visit 1.
6. Target ulcer with exposure of tendon, muscle or bone.
7. Medical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.

### 7.4 SCREENING LOG

The site is required to document all screened subjects (those who have provided informed consent) initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and noted on the Screening Log.

## 8. STUDY DESIGN

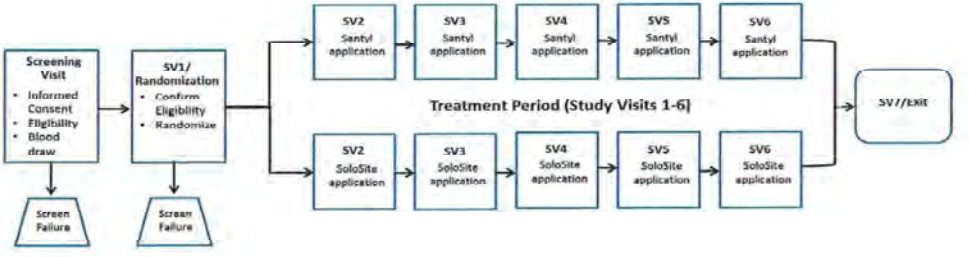
### 8.1 STUDY DESIGN

This is a randomized, controlled, parallel observer-blind group study. Subjects providing informed consent will be screened against the inclusion/exclusion criteria. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomly assigned in an equal allocation ratio (1:1) to either SANTYL or to the hydrogel control according to a pre-determined randomization schedule using a blocking technique. Subject randomization will be stratified by the Subject's wound size at baseline resulting in two possible strata: $\geq$1.0 and $\leq$10.0 $cm^2$; and >10.0 and $\leq$64.0 $cm^2$. A blocked design will be used for each individual stratum. In either case, caregivers will apply test article once daily (more often as needed for compromised dressing integrity) for up to 6 weeks.

If the ulcer is closed and completely re-epithelialized prior to the end of the 6 week treatment period in either group, the subject will complete Study Visit 7 (Exit) and will be dismissed from the study.

At each weekly visit, the target ulcer will be photographed and area measured using the ImageIQ EDCIQ mobile imaging system. At Study Visit 1 and at Study Visit 7, the ulcer will be assessed using the PUSH and WBS tools. In addition, resource utilization information will be collected at each study visit as described in Section 9.5.

**Figure 8.1-1: Study Flow Chart**




## 8.2 Methods Used to Minimize Bias

Due to obvious differences in the physical appearance of the test articles, double-blinding of the study medication is not possible. However, assessments of the ulcer debridement status relating to the presence of non-viable necrotic tissue (primary objective) will be carried out in a blinded fashion by two independent assessors using digital photographs identified only by the subject number and date. Blinded assessment is intended to limit the occurrence of conscious and unconscious bias in the assessment and interpretation of the endpoints. In addition, randomization will be sequential according to a pre-determined, computer-generated randomization schedule. In this way the Investigator will not be able to direct a particular subject to a particular treatment thus preventing treatment allocation bias. Ulcer measurements will be carried out using the ImageIQ EDCIQ mobile imaging system which will minimize subjectivity in theses assessments.

# 9. STUDY PROCEDURE

For a summary of the required procedures by visit, refer to Table 17-1: *Study Procedures by Visit*.

## 9.1 VISITS AND EXAMINATIONS

### 9.1.1 Screening Visit (SCR)

***NOTE***: Any subject who signs an informed consent, but fails to meet the required entry criteria is considered to be a Screen Failure. Their demographic information must be captured in the Eligibility CRF with the reason for screen failure specified.

1. Explain the purpose and nature of the study, and have the subject or the subject's legally-authorized representative **read**, **sign**, and **date** the IRB-approved informed consent document. In addition, the informed consent document must be signed and dated by the individual who consents the subject. Provide a photocopy of the signed informed consent document to the subject or subject representative, and place the original signed document in the subject's medical record.

   ***—— Do not proceed until consent has been obtained ——***

2. Assign a subject ID number (format xx-yyy, where xx=01, the two-digit site number, and yyy=three-digit sequential subject number).
3. Obtain demographic information and medical history, including information on all concomitant medications.
4. Photograph the target ulcer using the ImageIQ EDCIQ mobile imaging system (refer to Section 9.4.1).

   Target ulcer area must be between 1.0 $cm^2$ and 64.0 $cm^2$ (inclusive) and have at least 85% of the surface covered with necrotic, nonviable tissue as assessed by at least one independent image reviewer.
5. If the ulcer is on a lower extremity, obtain ABI for the target ulcer limb. ABI must not be less than 0.85.

6. Screen the subject for protocol inclusion and exclusion criteria. If the subject does not meet ALL inclusion criteria or does meet ANY exclusion criterion, the subject must be dismissed as a screen failure.
7. Obtain a venous blood sample for serum pre-albumin and hemoglobin A1c measurements (send blood to local laboratory for analysis).

   **Note**: If an HbA1c or pre-albumin test has been conducted within the last 30 days and is recorded in the subject's chart, an additional test is not required.
8. Conduct a urine pregnancy test for women of childbearing potential.
9. If any adverse events are observed or reported due to study-mandated procedures (e.g., venous blood sample), the events must be reported as instructed in Section 12, *Adverse Events*.
10. Study Visit 1 should be scheduled within 7 days of the Screening Visit.

### 9.1.2 Randomization/Study Visit 1

This visit should occur no more than 7 days after the Screening Visit. Any subject who returns but does not qualify at this visit will be a screen failure and will not be randomized. Upon completion of all screening procedures and confirmation that the subject is eligible for the study, the Investigator or designee will randomize the subject using an electronic randomization system (www.sealedenvelope.com) to obtain the treatment assignment.

The day of the week (Monday, Tuesday, etc.) on which this visit occurs will set the weekly visit day for all subsequent assessments/visits (Study Visits 2 through 7) if the subject is randomized. A (±1) day visit window will be allowed. If an assessment is not made on the original day of the week for Study Visits 2–7, subsequent visits should be scheduled on the original week day.

To minimize differences in baseline ulcer size between the two groups, randomized subjects will be stratified by ulcer size determined at this visit [$\geq$1.0 and $\leq$10.0 $cm^2$; >10.0 and $\leq$64.0 $cm^2$].

Once randomized, subjects will be assessed weekly for the duration of the treatment period (SV1 through SV7).

The following procedures will be completed:

1. Record any changes in general health and the use of concomitant medications.
2. If any adverse events are observed or reported, they must be recorded as instructed in Section 12, *Adverse Events*.
3. Review laboratory results from the blood sample and all other inclusion/exclusion criteria.

   If the blood test results qualify and all entry criteria are met, the subject may be randomized.
4. Irrigate the wound with normal saline delivered at 4-15 psi using the Irrimax® device. (Sharp debridement is NOT allowed.)
5. Photograph the target ulcer using the ImageIQ EDCIQ mobile imaging system. The target ulcer area ($cm^2$) and percentage of the target ulcer surface covered with necrotic, nonviable tissue will be determined by two independent reviewers using the ImageIQ EDCIQ mobile imaging system. The target ulcer area and percentage of necrotic, nonviable tissue must be assessed by at least one independent reviewer prior to the subject being randomized.

   **Note:** If the area of the target ulcer is >64.0 $cm^2$, the subject must be screen failed and should not be randomized.
6. Assess the wound status using both the PUSH and WBS tools.
7. Apply the test article to the entire wound bed according to the instructions for use located in the Study Guide, cover with a semi-occlusive dressing (e.g. COVRSITE™). If the wound has depth, saline-moistened gauze may be used to fill at the Investigator's discretion.
8. Ensure that all caregivers are instructed as to the treatment requirements for the study protocol and that they are instructed in the application of test article and dressing changes.

Ensure adequate supplies (test article and dressings) are dispensed.

9. Record the time spent dressing the ulcer at this visit.
10. Schedule the assessment, Study Visit 2, in 7 (±1) days.

### 9.1.3 Study Visits 2-6

Study Visits 2-6 are post-randomization weekly assessments during the treatment period. During this period, all adverse events must be recorded, including those associated with treatment, study procedures, or concomitant medication. All weekly visits must be performed according to the study visit schedule (Table 17-1), preferably on the same day each week. Subjects found to have wound closure at a weekly assessment should **NOT** complete that visit but instead go directly to Study Visit 7 (Exit Visit), be discontinued from treatment and have exit procedures performed. A closed ulcer is defined as having complete re-epithelialization, without drainage or the need for a dressing. All study procedures should occur in the order outlined in the protocol. Visits occurring outside the visit window should be completed and recorded as a protocol deviation.

1. If the ulcer is closed at this assessment visit, do not complete these procedures. Instead go directly to Study Visit 7 (Exit Visit).
2. Record any changes in general health and the use of concomitant medications.
3. If any adverse events are observed or reported, they must be recorded as instructed in Section 12, *Adverse Events*.
4. Record the number of dressing changes since the previous study visit and the amount of time spent daily dressing the ulcer.
5. Irrigate the wound with normal saline delivered at 4-15 psi using the Irrimax® device. (Sharp debridement is NOT allowed.)
6. Photograph the target ulcer using the ImageIQ EDCIQ mobile imaging system. The target ulcer area ($cm^2$) and percentage of the target ulcer surface covered with necrotic,

nonviable tissue will be determined by two independent reviewers using the ImageIQ EDCIQ mobile imaging system.

7. Ensure that all caregivers are instructed as to the treatment requirements for the study protocol and that they are instructed in the application of test article and dressing changes. Ensure adequate supplies (test article and dressings) are dispensed.
8. Apply the test article to the entire wound bed according to the instructions for use located in the Study Guide, cover with a semi-occlusive dressing (e.g. COVRSITE™). If the wound has depth, saline moistened gauze may be used to fill at the Investigator's discretion.
9. Record the time spent dressing the ulcer at this visit.
10. Schedule the next weekly assessment in 7 (±1) days.

### 9.1.4 Exit Visit – Study Visit 7

This is the final visit for all subjects in the study.

1. Record any changes in general health and the use of concomitant medications.
2. If any adverse events are observed or reported, they must be recorded as instructed in Section 12, *Adverse Events*.
3. Record the number of dressing changes since the previous study visit and the amount of time spent daily dressing the ulcer.

***Only if the ulcer remains open at this visit:***

4. Irrigate the wound with normal saline delivered at 4-15 psi using the Irrimax® device. (Sharp debridement is NOT allowed.)

***All subjects:***

5. Photograph the target ulcer using the ImageIQ EDCIQ mobile imaging system. The target ulcer area ($cm^2$) and percentage of the target ulcer surface covered with necrotic, nonviable tissue will be determined by two independent reviewers using the ImageIQ EDCIQ mobile imaging system. Closed ulcers will be photographed and designated as "closed".
6. Assess the wound status using both the PUSH and WBS tools.
7. Record the time spent assessing the ulcer.
8. All females of child-bearing potential must undergo a urine pregnancy test upon completion or discontinuation from the study.
9. Return all used and unused study medication to a secure area for accountability.
10. Dismiss the subject from the study. Institute appropriate standard ulcer care for ulcers remaining open at the discretion of the Investigator.

### 9.1.5 Unscheduled Visits

Unscheduled exams may be conducted at the discretion of the Investigator with all obtained information recorded in the source documents and on the Unscheduled Visit pages within the Case Report Form (CRF).

### 9.1.6 Concomitant Medications

A concomitant medication is any drug or substance administered from Day 1 (SCR 1) of the study through the last study visit. No therapies other than the assigned test article are to be used to treat the target ulcer during the study period. These include:

- Oral steroid use > 5 mg daily
- Growth factors

- Living skin equivalents (e.g. Apligraf®, Dermagraft®)
- Extracellular matrix products (e.g. OASIS®)
- Amniotic membrane products
- Any target ulcer treatment, excluding study treatment, specifically intended to close the wound (topical antibiotics are acceptable if needed but study treatment should be withheld and doses would be considered as missed).

The use of concomitant medications used to treat the ulcer and any medications used for the treatment of adverse events must be recorded. Adverse events related to administration of these therapies must be documented appropriately.

## 9.2 Discontinued Subjects

Discontinued subjects are those who voluntarily discontinue participation, who are withdrawn for safety reasons or use of prohibited concomitant treatments. In all cases the Exit Visit (Study Visit 7) must be completed.

All subjects who discontinue the study prior to completing the regularly-scheduled visits should complete the exit visit procedures described in Section 9.1.4. If appropriate, the Investigator also should advise the subject of subsequent therapy and/or procedures necessary for their medical condition.

## 9.3 Subject Pregnancy

Women of child-bearing potential are not excluded from the study provided they are not pregnant at screening as documented by a negative urine pregnancy test. However, if a woman becomes pregnant during the study, Smith & Nephew should be contacted immediately and a decision will be made regarding the continuation in the study of the pregnant woman. Pregnancy is not reportable as an adverse event; however, complications related to the pregnancy may be reportable as determined on a case-by-case basis. Pregnancy-related information will be collected until termination of the pregnancy.

## 9.4 STUDY METHODS AND MEASUREMENTS

### 9.4.1 Wound photography and measurement

All wound photographs and measurements will be taken with the ImageIQ EDCIQ mobile imaging system. The system utilizes a portable device (e.g., iPad) that easily allows capture of wound images. Once captured the images are sent to a central database for storage and review. Quantitative measurements and other wound assessment data will be inputted into the EDCIQ system by the independent reviewers. ImageIQ builds that information into an electronic record for review and archiving. Information about the wound's measurement history is available on this system so that the serial progression of wound status can be calculated and presented.

### 9.4.2 Percentage of Necrotic Tissue and "Complete Debridement"

All wound photographs will be reviewed in a blinded fashion, identified only by subject number, initials, and date of assessment by two independent reviewers. The reviewers will complete an assessment form providing the percentage of the ulcer covered by non-viable, necrotic tissue as measured using the ImageIQ EDCIQ mobile imaging system. In any case where one reviewer selects 0% or "complete debridement", and the second reviewer does not, the photograph will be re-reviewed at a consensus meeting.

### 9.4.3 Wound Assessment Scales

The PUSH Tool (Version 3.0), specifically developed for pressure ulcers, and the WBS will be used to assess all ulcers at baseline (Study Visit 1), and at Exit. Copies of these instruments are included in the appendices.

## 9.5 HEALTH ECONOMICS

Resource utilization information will be collected at each dressing change throughout the study. More specifically, investigators will provide the amount of time, in minutes, dedicated to each dressing change via a log within the electronic case report form (eCRF). Additionally, the per-patient quantity of test articles utilized will be documented according to the test article

accountability procedures of the protocol as described in Section 6.4. Non-test article wound care supplies such as spatulas, gauze, and secondary dressings are standardized for each dressing change and thus no direct documentation of utilization for these items will be collected. This information will be used to examine resource utilization rates between treatment groups.

## 10. STATISTICAL DESIGN

A formal Statistical Analysis Plan (SAP) (also referenced to as the Statistical Considerations) will be written and finalized prior to database lock. The SAP will detail the summaries and analyses to be performed.

Smith & Nephew Wound Management Global Medical and Clinical Affairs Department will conduct data management and statistical analysis. Unless otherwise stated, all significance tests and hypothesis testing will be two-sided, performed at the 5% significance level. Resulting p-values will be quoted and 95% two-sided confidence intervals will be generated where appropriate. All analyses will be performed in SAS v9.4 (or later).

Where data summaries are specified, categorical and ordinal variables will be summarized using frequency distributions which will detail the number and percentage of subjects which fall into each category. Continuous variables will be summarized using the following summary statistics: mean, median, standard deviation, minimum and maximum values, and number of observations.

### 10.1 EVALUABILITY

All subjects who provide informed consent and complete a screening visit are considered study participants. Study populations are defined as follows, with statistical analysis performed separately on each of the populations:

- Safety population, including all subjects who are randomized and have received at least one treatment of test article.
- Intent-to-treat (ITT) population (otherwise referred to the as the Full Analysis Set), including all subjects who are randomized, have a valid baseline ulcer measurement, and

complete at least one post-baseline visit. The ITT population is the primary efficacy population.

- Per protocol (PP) population, including those ITT subjects who complete the 6-week treatment period (or achieve a closed ulcer in < 6 weeks), receive only the initially-randomized treatment, have no significant protocol deviations, and meet the pre-randomization inclusion/exclusion criteria. The PP population is the secondary efficacy population.

### 10.2 Handling of Missing and Incomplete Data

The methods used to handle missing or incomplete data for the efficacy and safety measures will be detailed in the Statistical Analysis Plan. For purposes of the primary endpoint, in cases where a photograph is not taken, the Last Observation Carried Forward (LOCF) method will be used. Sensitivity analyses will be conducted as detailed in the following sections to examine the impact of these derivations on the conclusions relating to the primary endpoint.
For purposes of assessments of wound area (and subsequent reductions over the study period), in cases where Study Visit 7 is not attended by the subject, or the area value at the assessment is not recorded or known, the Last Observation Carried Forward (LOCF) method (excluding Study Visit 1) will be used.

### 10.3 Efficacy

#### 10.3.1 Primary Efficacy

The primary endpoint of the study is the proportion of subjects achieving complete debridement over the 6-week treatment period and will be analyzed as follows using the Full Analysis Set. For purposes of the primary analysis, the status of complete debridement will be assessed from photographs by two independent reviewers. In the event of disagreement between the two reviewers, the complete debridement status agreed during the consensus meetings will be analyzed in the primary analysis. In cases where a photograph is not taken, the Last Observation

Carried Forward (LOCF) method will be used. Sensitivity analyses will be conducted as detailed in the following sections.

An initial logistic regression model will contain covariates for treatment, baseline (defined as Study Visit 1) ulcer area, baseline percentage of nonviable tissue, and duration of ulcer. A forward selection procedure will be used for the addition of other baseline covariates with an F-value to attain a significance level of 0.1. Further baseline covariates to be assessed as part of this procedure include: subject age, baseline (maximum) ulcer depth, baseline PUSH and WBS scores.

The resulting analysis presented will correspond to the final model from the forward selection procedure. The results for the initial model will also be presented. For each of the effects in the initial and final model, the p-value, odds-ratio and corresponding 95% confidence interval will be presented. Secondary subgroup analyses may be conducted as a result of the covariate analyses. Additionally, treatment will be fitted on its own in a further logistic regression model. In each case, the residuals will be examined for outliers using influence plots of diagnostic statistics; further details are included in the SAP.

Cross-tabulations of each of the covariates (continuous covariates will be categorized for purposes of the cross-tabulations) with treatment and achievement of complete debridement, will be generated for each of the baseline covariates included in the final model.

The 95% confidence interval (unadjusted for all covariates) for the difference between treatments in proportion achieving complete debridement within 6 weeks will be generated along with the Chi-square or Fisher's Exact test p-value using the Per Protocol population depending on minimum expected cell.

Two separate sensitivity analyses will be performed to ensure that the efficacy findings are not reliant on assumptions made in the analysis, derivations, or changes agreed between the blinded review panel. The analysis for the proportion of subjects achieving completed debridement will be repeated with the following modifications using the Full Analysis Set only:

1) In cases where there is initial disagreement (pre-consensus meeting) between the two blinded reviewers, the "worst case" value will be used. That is, in cases where one reviewer found the ulcer to have achieved complete debridement whilst the remaining reviewer found there to still be (>0%) necrotic, non-viable tissue present, the following will be imputed:

Complete debridement achieved = No.

2) In cases where there is initial disagreement (pre-consensus meeting) between the two blinded reviewers, the "best case" value will be used. That is, in cases where one reviewer found the ulcer to have achieved complete debridement whilst the remaining reviewer found there to still be (>0%) necrotic, non-viable tissue present, the following will be imputed:

Complete debridement achieved = Yes.

### 10.3.2 Secondary Efficacy

The secondary efficacy variables include the time (in days) to achieve complete debridement, the percentage reduction in non-viable necrotic tissue for each assessment visit, and the percentage reduction in ulcer area for each visit and the change in wound status as measured by the PUSH and WBS tools following 6 weeks of treatments.

**Time (in days) to achieve complete debridement during the 6-week treatment period (with complete debridement as defined in the primary analysis)**

Once a subject has achieved complete debridement, the time to complete debridement will be calculated from the date of the randomization visit to the date at which the subject's ulcer was deemed to achieve complete debridement:

$$(\,Date\ of\ first\ complete\ debridement\ visit - Date\ of\ Randomization\ (SV1)\,)$$

For those subjects that withdraw or do not achieve complete debridement during the study, the time to complete debridement will be censored at the last visit date attended. The resulting time to complete debridement will be defined as:

$$(\,Date\ of\ Last\ Study\ Visit\ attended - Date\ of\ Randomization\ (SV1)\,)$$

Where the censored time to complete debridement is greater than 42 days, this will be truncated to 42 days.

A proportional hazards survival analysis will be applied to the time to achieve complete debridement using the Full Analysis Set. An initial proportional hazards model will include the covariates for treatment, baseline (defined as Study Visit 1) ulcer area, baseline percentage of nonviable tissue, and duration of ulcer. A forward selection procedure will be used for the addition of other baseline covariates with an F-value to attain a significance level of 0.1. Further baseline covariates to be assessed as part of this procedure include: subject age, baseline (maximum) ulcer depth, baseline PUSH and WBS scores. The resulting analysis presented will correspond to the final model from the forward selection procedure. The results for the initial model will also be presented. For each of the effects in the initial and final model, the p-value, hazard-ratio and corresponding 95% confidence interval will be presented. Secondary subgroup analyses may be conducted as a result of the covariate analyses. Additionally, treatment will be fitted on its own in a further proportional hazards survival analysis.

Further details, including model assumptions and diagnostics to be examined are included in the study SAP. The preceding analysis will be repeated using the Per Protocol Population.

Kaplan-Meier plots will be presented by treatment, baseline wound area strata, baseline percentage of nonviable tissue and ulcer duration (categorized) and also to represent all covariates with significant effects in the final survival analysis model. Individual plots for multiple factors will be generated where appropriate.

In addition, a sensitivity analysis will be performed to ensure that the efficacy findings are not reliant on assumptions made in either the analysis or derivations. For purposes of the sensitivity analysis, the time to confirmed complete debridement for those subjects discontinuing the treatment period prematurely will be censored at the maximum possible duration of treatment under the study protocol (42 days), rather than time of actual discontinuation. Lastly, the two sensitivity analyses defined in the proportion of subjects achieving complete debridement analysis will be repeated for the time to achieve complete debridement; in these cases the

censoring flag may be modified as detailed previously in the primary analysis, but the time in days will remain unchanged.

**The percentage reduction in wound area over the 6-week treatment period and at each assessment visit**

Wound area is defined as surface area as measured by the ImageIQ EDCIQ mobile imaging system at each assessment visit by two independent image reviewers. The percentage change in wound area over the 6-week treatment period is then defined as:

$$\text{Percentage reduction in wound area over 6-week treatment period} = \left( \left( \frac{Area_{SV1} - Area_{SV7}}{Area_{SV1}} \right) \times 100 \right)$$

In cases where the wound is closed in the opinion of the Investigator, the wound area will be imputed as 0 $cm^2$, resulting in a percentage reduction in wound area of 100%. In circumstances where the wound area is missing at the Study Visit 7 for subjects that have not withdrawn prematurely due to closure, the last observation carried forward (LOCF) method will be used.

An initial linear regression model will contain covariates for treatment, baseline (defined as Study Visit 1) ulcer area, baseline percentage of nonviable tissue, and duration of ulcer. A forward selection procedure will be used for the addition of other baseline covariates with an F-value to attain a significance level of 0.1. Further baseline covariates to be assessed as part of this procedure include: subject age, baseline (maximum) ulcer depth, baseline PUSH and WBS scores. The resulting primary analysis presented will correspond to the final model from the forward selection procedure. The results for the initial model will also be presented. For each of the effects in the initial and final model, the p-value, parameter estimate and corresponding 95% confidence interval will be presented. Secondary subgroup analyses may be conducted as a result of the covariate analyses. Additionally, treatment will be fitted on its own in a further linear regression model. The potential for interactions will be examined by fitting the required interaction terms in addition to those effects in the final linear regression model from the forward selection procedure. In each case if the residuals are not normally distributed then non-parametric bootstrapping will be applied. If the nonparametric bootstrap estimates of the confidence intervals for the difference in mean percentage reduction in area between treatments

differ considerably to the standard model estimates, then the nonparametric bootstrap estimates will be used.

The percentage reduction in wound area over the 6-week treatment period will be summarized by treatment separately by the covariates used in the final model.

In addition, a two-sample t-test will be used to test for a difference between treatments in the mean percentage reduction in wound area between Visit 1 and Visit 2. The test will be repeated for comparisons between Visit 1 and Visits 3, 4, 5 and 6 individually. In each case, if normality assumptions do not hold, a Wilcoxon Rank Sum test will be used.

The wound area, reduction in wound area and percentage reduction in wound area at each study visit will be summarized by treatment separately by baseline wound area strata and overall.

**The reduction in percentage non-viable necrotic tissue over the 6-week treatment period and at each assessment visit**

For purposes of the analysis, the assessment of percentage non-viable necrotic tissue will be assessed from photographs by two independent reviewers. The following analysis uses the mean of the two percentage non-viable tissue assessments conducted by the independent reviewers for each visit. In the event of disagreement between the two reviewers, the percentage non-viable necrotic tissue used in the following analysis will be the mean of the individual assessments of non-viable necrotic tissue after any consensus meetings have been conducted.

The reduction in the percentage non-viable necrotic tissue will be derived as:

Percentage non-viable necrotic tissue at Study Visit 1 – Percentage non-viable necrotic tissue at Study Visit 7

In cases where a photograph is not taken, the Last Observation Carried Forward (LOCF) method will be used. Sensitivity analyses will be conducted as detailed in the following sections.

The linear regression analysis described in the previous section to test for a difference between treatments in the percentage reduction in wound area over the 6-week will be repeated for the reduction in percentage of non-viable necrotic tissue over the 6-week treatment period. In addition, the separate analysis conducted to test for a difference in percentage reduction in

wound area between treatments between Visit 1 and Visits 2,3,4,5 and 6 will be repeated for the reduction in percentage of non-viable necrotic tissue at the stated time points.

The reduction in percentage non-viable necrotic tissue over the 6-week treatment period will be summarized by treatment separately by the covariates used in the final model. In addition, the percentage non-viable necrotic tissue and reduction percentage non-viable necrotic tissue at each study visit will be summarized by treatment separately by baseline percentage necrotic tissue [categorized] and overall.

Two separate sensitivity analyses will be performed to ensure that the efficacy findings are not reliant on assumptions made in the analysis, derivations or changes agreed between the blinded review panel. The previous section will be repeated with the following modifications using the Full Analysis Set only:

1) The "worst case" value will be used. That is, the highest value of percentage non-viable necrotic tissue recorded by the two independent reviewers at each time point will be used for purposes of analysis.

2) The "best case" value will be used. That is, the lowest value of percentage non-viable necrotic tissue recorded by the two independent reviewers at each time point will be used for purposes of analysis.

**Change in Wound Status as measured by the PUSH and WBS tools following 6 weeks of treatment**

Wound status will be measured by both the PUSH and WBS tools at Study Visit 1 and at Study Visit 7 (Exit).

At both Study Visit 1 and Study Exit, the PUSH Tool (version 3.0) will be scored according to the instructions for use (18.1.1). The sub-scores for Length/Width, Exudate Amount, and Tissue Type will be recorded. The Total Score, on a scale of 0-17, will then be derived by taking the sum of the three sub-scores detailed previously.

The reduction in PUSH individual sub-scores will be derived as follows; the reduction in Total Score will be derived using the same method:

*PUSH Score at Visit 1 – PUSH Score at Exit Visit*

A Wilcoxon Rank Sum test will be used to test for a difference between treatments in the reduction in Total PUSH Score over the 6-week treatment period.

The responses to the individual sub categories (Length/Width, Exudate Amount, and Tissue Type) will be summarized by treatment at each visit; in addition the reduction over the 6-week treatment period in each sub-score and total score will be summarized by treatment.

The WBS will be scored at the Study Visit 1 and Study Exit according to the instructions for use (18.1.2). The individual wound bed score characteristics, on a scale of 0-2, will be summed to derive the Total WBS on a scale of 0-16.

The reduction in Total WBS will be derived as follows:

*Total WBS Score at Visit 1 – Total WBS Score at Exit Visit*

A Wilcoxon Rank Sum test will be used to test for a difference between treatments in the reduction in Total WBS over the 6-week treatment period.

The responses to the individual wound bed score characteristics (Healing edges, Black eschar, etc.) will be summarized by treatment at each visit.

### 10.3.3 Exploratory Analysis

The exploratory analysis for this study will be a comparison of resource utilization for each treatment group. Resource utilization in the form of nursing time spent on dressing changes, test article utilization, and wound care supplies utilized will be aggregated with descriptive statistics reported by treatment group.

### 10.4 SAFETY

Safety variables include adverse events (AE). AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The treatment-emergent AEs will be reported separately for the 6-week treatment period (Study Visits 2 to 7) and initial screening period (interval between Screening Visit 1 and Screening Visit 2). Frequency of treatment-emergent AE will be calculated for each body system, by preferred term, by subject group (i.e., SANTYL, hydrogel), for number of subjects and proportion reporting the event for the safety population. The severity of the AE and the relationship to study medication will be summarized for each body system and preferred term by subject group. Withdrawals in general and withdrawals due to AE will be summarized for each body system and preferred term by subject group.

## 11. SAMPLE SIZE JUSTIFICATION

A previous study (7) with a design essentially identical to the present study demonstrated highly significant differences between treatment groups for achievement of complete debridement (85% vs. 29%, $P<0.003$), reduction in % area of non-viable tissue for each week ($P<0.002$), and in reduction in wound area ($P<0.009$). The sample size of this previous trial was 27 subjects, 13 in the SANTYL group, and 14 in the hydrogel group. Based on the reported outcomes in the previous trial, 26 subjects are required to detect a difference in the primary endpoint: the proportion of ulcers achieving complete debridement during the 6-week treatment period. This relates to a Fisher's Exact test assuming 85% vs 29% in the proportion of ulcers achieving complete debridement. To allow for 15% drop-out rate throughout the 6-week treatment period, a total of 32 subjects will be randomized (16 per treatment) in an equal allocation ratio for SANTYL and hydrogel. In the previous studies quoted, the secondary endpoints including reduction in % area of non-viable tissue and reduction in wound area were found to reach significance with similar numbers.

# 12. ADVERSE EVENTS

## 12.1 General Information

An AE is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

Adverse drug reactions (ADR) are noxious and unintended responses to a medicinal product, meaning that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected.

## 12.2 Non-serious Adverse Events

A non-serious AE is defined as a change from baseline (pre-treatment) in a subject's medical health that is not life-threatening, does not require hospitalization, does not prolong a current hospitalization, and is not disabling. Non-serious AE must be reported to Smith & Nephew by use of an Adverse Event Form. All non-serious AE must be reported in the subject's source documents. AE associated with the target ulcer must be recorded on an Adverse Event Form in the source and eCRF regardless of whether or not they are considered to be related to the test article. AE related to the test article must also be recorded on an Adverse Event Form in the source and eCRF.

## 12.3 Serious Adverse Events

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (*NOTE*: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the

event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe)

- Requires inpatient hospitalization or results in prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically-important event or reaction

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

### 12.4 Reporting of AE and SAE

AE associated with the target ulcer and all SAE of any kind will be recorded in the AE eCRF. For each recorded event, the eCRF must include the event's onset and resolution date (if the event has resolved), the frequency and severity of the event, a summary of any action taken as a result of the event (both in regard to any treatment given and to any change in dosing with the test article), and an assessment of the event's relationship to the test article. AE judged to be related to the test article and all SAE will be entered into the eCRF and reported to the Sponsor within 24 hours of knowing about the event. Target ulcer AE judged not related to the test article will be entered into the safety database within 48 hours of the site becoming aware of the event. All SAE and test article-related AE will be reviewed by the Medical Monitor and the Medical Reviewer to determine which, if any, meet expedited reporting criteria. All events requiring expedited reporting will be forwarded to Regulatory by the Medical Reviewer for further processing.

A Serious Adverse Event Form must be completed for all SAE and forwarded to Smith & Nephew within 24 hours of the Investigator's knowledge of the event and to the Institutional Review Board/Independent Ethics Committee, according to their requirements. When new significant information is obtained as well as when the outcome of an event is known, the Investigator must provide Smith & Nephew with this information as soon as it becomes available. Depending on the nature of the AE, Smith & Nephew may request copies of the subject's medical records as well as results of any relevant laboratory tests performed. If the subject was hospitalized, a copy of the discharge summary may be requested by Smith & Nephew and should be forwarded as soon as it becomes available. In certain cases, Smith & Nephew also may request a letter from the Investigator that summarizes the events related to the case.

SAE must be reported using the eCRF system (preferred), or via telephone or fax, to one of the following Smith & Nephew representatives within 24 hours of the Investigator's knowledge of the event:

**Table 12.4-1: Study Contact Information**

| | | |
|---|---|---|
| Jaime E. Dickerson, PhD<br>Medical Monitor | Business Phone<br>Business Fax<br>Mobile Phone | 817-302-3914<br>817-887-0721<br>817-845-0859 |
| Alain Rohan, MBBS, MPH<br>Medical Reviewer | Business Phone<br>Business Fax<br>Mobile Phone | 817-302-3902<br>817-887-0721<br>817-751-0053 |

## 12.5 Adverse Event Severity and Causality Assessment

Events should be classified as mild, moderate, or severe, regardless of whether or not the events are considered to be serious or nonserious. The classification should be based on the following definitions:

**Mild** – An event is mild if the subject is aware of, but can easily tolerate the sign or symptom

**Moderate** – An event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities

**Severe** – An event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities

In addition, the Principal Investigator will determine AE causality according to the following definitions and with due consideration to conditions and AE normally associated with the population under study:

**Not Related** – An event is considered to be not related to the use of the test article when the event is DEFINITELY UNRELATED or UNLIKELY to have any relationship to the use of the test article

**Possibly Related** – An event is considered to be possibly related to the use of the test article when there is a REASONABLE POSSIBILITY that the test article caused the AE

For example, a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens - Johnson syndrome) has a reasonable possibility of association with the test article. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the test article, may have a reasonable possibility of association. AE which are known to be common in the population under study would require additional evidence (e.g., strong temporal relationship, recurrence on re-challenge, unusual severity, and/or increasing frequency) before being considered possibly related.

## 12.6 UNBLINDING OF TEST ARTICLE

Not Applicable

## 12.7 FOLLOW-UP OF SUBJECTS WITH ADVERSE EVENTS

For subjects who are experiencing ongoing unresolved AE at the time of their study completion or early discontinuation from the study, it is recommended that the Investigator schedule an appropriate follow-up visit in order to determine the outcome of the event. Any additional data

must be documented and available to the sponsor who will determine when the data need to be documented on the case report forms.

## 13. INVESTIGATOR OBLIGATIONS

The Principal Investigator will comply with the commitments outlined in the Statement of Investigator (Form FDA 1572), with current Good Clinical Practice (GCP), and with all applicable regulatory requirements as outlined in Appendix 18.3 of this protocol.

## 14. SPONSOR AND MONITOR RESPONSIBILITIES

The Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored to ensure that: the rights and well-being of the subjects are protected; the reported data are accurate, complete, and verifiable from the source documents; and the study is conducted in compliance with the current approved protocol [and amendment(s), if applicable], with current GCP, and with applicable regulatory requirements.

All studies will have a site initiation. Monitoring will be conducted periodically while the clinical study is ongoing. Monitoring methods may include site visits, telephone, written and fax correspondence. The Study Manager and/or assigned study monitor will contact each site at appropriate intervals. The Study Manager will determine the frequency of site visits. Close-out visits will take place after the last visit of the last subject.

## 15. CONFIDENTIALITY OF THE STUDY

The confidentiality of this study and associated documents is governed by the terms of the Clinical Trial Agreement.

## 16. REFERENCES

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(8) Tallis A, Motley TA, Wunderlich RP, Dickerson JE Jr, Waycaster C, Slade HB. Clinical and economic assessment of diabetic foot ulcer debridement with collagenase: results of a randomized controlled study. Clin Ther 2013;35:1805-20.

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## 17. STUDY PLAN

**Table 17-1: Study Procedures by Visit**

| | Screening Period | Treatment Period Weekly Visits (±1 day) | | Exit |
|---|---|---|---|---|
| **Procedures** | **Screening Visit** | **Study Visit 1[a]** | **Visits 2-6** | **Study Visit 7** |
| Informed Consent | X | | | |
| Demographics/Medical History | X | | | |
| Inclusion/Exclusion | X | X | | |
| Irrigation of ulcer | | X | X | X[b] |
| Photography and Measure Ulcer Size | X | X | X | X[c] |
| Ankle brachial index[d] | X | | | |
| Blood collection (pre-albumin, HbA1c)[e] | X | | | |
| Urine Pregnancy Test[f] | X | | | X |
| PUSH assessment | | X | | X |
| WBS assessment | | X | | X |
| Application of Study Treatment | | X | X | |
| Determine/record nursing time at this visit | | X | X | X |
| Record Adverse Events | X | Assessed throughout the study | | |
| Concomitant Medications | X | Assessed Throughout the study | | |

a Study Visit 1 should occur within 7 days of the Screening Visit.
b Not applicable if ulcer is closed.
c Photograph ulcer area even if ulcer is closed.
d Only if ulcer is on a lower extremity.
e HbA1c and pre-albumin are required unless a test has been carried out and recorded in chart within 30 days of SCR1
f Must be conducted on all women of child-bearing potential, including those who have had a bilateral tubal ligation.

# 18. APPENDICES

## 18.1 INSTRUMENTS AND SPECIAL INSTRUCTIONS

### 18.1.1 PUSH Tool version 3.0

The Pressure Ulcer Scale for Healing (PUSH) Tool (12) is a validated instrument that comprises three subscale scores used to assess PU healing: 1) ulcer size (scored on a scale of 0 to 10 points), 2) exudate (scored on a scale of 0 to 3 points), and 3) type of the tissue (scored on a scale of 0 to 4 points). The three subscale scores are added to generate a cumulative wound status score. A cumulative score of 17 indicates poorest PU status and a score of 0 indicates the best possible status.

## Figure 18.1-1: PUSH Tool Version 3.0

NATIONAL PRESSURE ULCER ADVISORY PANEL

**Pressure Ulcer Scale for Healing (PUSH)**
**PUSH Tool 3.0**

Patient Name _____ Patient ID# _____

Ulcer Location _____ Date _____

**Directions:**
Observe and measure the pressure ulcer. Categorize the ulcer with respect to surface area, exudate, and type of wound tissue. Record a sub-score for each of these ulcer characteristics. Add the sub-scores to obtain the total score. A comparison of total scores measured over time provides an indication of the improvement or deterioration in pressure ulcer healing.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **LENGTH X WIDTH** (in cm²) | **0**<br>0 | **1**<br><0.3 | **2**<br>0.3 – 0.6 | **3**<br>0.7 – 1.0 | **4**<br>1.1 – 2.0 | **5**<br>2.1 – 3.0 | **Sub-score** |
| | | **6**<br>3.1 – 4.0 | **7**<br>4.1 – 8.0 | **8**<br>8.1 – 12.0 | **9**<br>12.1 – 24.0 | **10**<br>>24.0 | |
| **EXUDATE AMOUNT** | **0**<br>None | **1**<br>Light | **2**<br>Moderate | **3**<br>Heavy | | | **Sub-score** |
| **TISSUE TYPE** | **0**<br>Closed | **1**<br>Epithelial Tissue | **2**<br>Granulation Tissue | **3**<br>Slough | **4**<br>Necrotic Tissue | | **Sub-score** |
| | | | | | | | **TOTAL SCORE** |

**Length x Width:** Measure the greatest length (head to toe) and the greatest width (side to side) using a centimeter ruler. Multiply these two measurements (length x width) to obtain an estimate of surface area in square centimeters ($cm^2$). Caveat: Do not guess! Always use a centimeter ruler and always use the same method each time the ulcer is measured.

**Exudate Amount:** Estimate the amount of exudate (drainage) present after removal of the dressing and before applying any topical agent to the ulcer. Estimate the exudate (drainage) as none, light, moderate, or heavy.

**Tissue Type:** This refers to the types of tissue that are present in the wound (ulcer) bed. Score as a "4" if there is any necrotic tissue present. Score as a "3" if there is any amount of slough present and necrotic tissue is absent. Score as a "2" if the wound is clean and contains granulation tissue. A superficial wound that is reepithelializing is scored as a "1". When the wound is closed, score as a "0".

- **4 – Necrotic Tissue (Eschar):** black, brown, or tan tissue that adheres firmly to the wound bed or ulcer edges and may be either firmer or softer than surrounding skin
- **3 – Slough:** yellow or white tissue that adheres to the ulcer bed in strings or thick clumps, or is mucinous.
- **2 – Granulation Tissue:** pink or beefy red tissue with a shiny, moist, granular appearance.
- **1 – Epithelial Tissue:** for superficial ulcers, new pink or shiny tissue (skin) that grows in from the edges or as islands on the ulcer surface.
- **0 – Closed/Resurfaced:** the wound is completely covered with epithelium (new skin).

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### 18.1.2 Wound Bed Score (WBS) (13)

| Wound bed score characteristics | 0 | 1 | 2 |
|---|---|---|---|
| Healing edges | None | 25–75% | > 75% |
| Black eschar | > 25% of wound surface area | 0–25% | None |
| Greatest wound Depth/granulation Tissue | Severely depressed or raised when compared to peri-wound skin | Moderate | Flushed or almost even |
| Exudate amount | Severe | Moderate | None/mild |
| Edema | Severe | Moderate | None/mild |
| Peri-wound Dermatitis | Severe | Moderate | None or minimal |
| Peri-wound Callus/fibrosis | Severe | Moderate | None or minimal |
| Pink wound bed | None | 50–75% | > 75% |

*The total WBS adds each individual score for each characteristic to give a total score. The maximum possible score (best score) is 16. The minimum possible score (worst score) is 0.

## 18.2 Additional Information

Not Applicable

### 18.3 PRINCIPAL INVESTIGATOR OBLIGATIONS

*References: ICH Guidelines for Good Clinical Practice (E6), and Code of Federal Regulations, 21 CFR, Parts 50, 54, 56, 312, 812.*

The Principal Investigator(s) must:

**1. Study Participants**

Ensure the protection of the rights, safety, and well-being of the study participants.

**2. Qualifications**

Be qualified by education, training, and experience to assume responsibility for the proper conduct of the study and provide documented evidence of such qualifications.

**3. Protocol**

Be thoroughly familiar with the Protocol, Protocol Amendment(s), and Clinical Investigators Brochure (CIB), and usage of the test article throughout the duration of the clinical study.

a. Sign the protocol agreeing to conduct the study according to the protocol.
b. Document and explain deviations from the protocol to the Sponsor and IRB/IEC, as required.
c. Inform the Sponsor and IRB/IEC within 24 hours if a protocol deviation is required to protect the safety of the patient.

**4. Resources and Staff**

Secure sufficient resources to conduct the study.

a. Devote sufficient time to properly conduct and complete the clinical study.
b. Oversee and assume responsibility for all sub-Investigators and site study personnel; assure that they are adequately trained and informed about the study protocol and investigational product; maintain a list of their delegated study-related activities.
c. Ensure that all instruments and equipment used in the study are maintained in good working order.

## 5. Regulatory Requirements

Comply with all applicable regulatory requirements to ensure Good Clinical Practice (GCP).

## 6. Study Participant Recruitment

Recruit, or demonstrate the appropriate effort to recruit, the required number of eligible study participants within the agreed recruitment period, based upon the established medical indication and the inclusion/exclusion criteria in the protocol.

## 7. Institutional Review Board / Independent Ethics Committees

Obtain written approval for the protocol (including protocol amendments) and the informed consent form (including informed consent revisions) from the Institutional Review Board (IRB) / Independent Ethics Committee (IEC).

a. Obtain IRB/IEC approval of subject recruitment materials and/or medium and any other information to be provided to potential study participants (e.g., instructions, brochures).
b. Submit copies of the IRB/IEC approval(s) to the Sponsor.
c. Obtain the name and address of the IRB/IEC and the membership roster or "Statement of Membership" from the IRB/IEC chairperson.
d. Maintain all records and correspondence to and from the IRB/IEC.
e. Submit periodic progress and final reports to the IRB/IEC at the frequency required by the IRB/IEC (at least yearly).
f. Obtain re-approval from the IRB/IEC as required.
g. Obtain IRB/IEC re-approval of revised Informed Consent documents and all applicable protocol amendments before their implementation.
h. Ensure that the IRB/IEC is organized and operates according to GCP and other applicable regulatory requirements.

**8. Informed Consent/Assent**

Obtain written informed consent and/or assent from each study participant (or legal representative) using the current IRB/IEC-approved Informed Consent Form (ICF) before performing any study-specific procedures on the study participant.

a. Ensure that the IRB/IEC-approved ICF is fully executed, including appropriate signatures, dates and other information.
b. Ensure that the written informed consent and any other written information to be provided to study participants is revised, approved by the IRB/IEC, disseminated to each study participant (or legal representative), and fully executed (including appropriate signatures, dates and other information) when new information becomes available that may be relevant to the study participant's consent.

**9. Adverse Events**

Report all AE to the Sponsor as specified in the protocol.

a. Ensure adequate medical care is provided to a subject for any AE.
b. Report all SAE to the Sponsor within 24 hours of the Investigator becoming aware of the occurrence whether the event is related or unrelated to the test article(s).
c. Report SAE to the IRB/IEC according to regulatory and IRB/IEC requirements

**10. Test Articles**

Maintain proper storage and control of all test articles.

a. Maintain a complete and accurate investigational test article inventory log. Accurately account for all investigational test articles received by the Investigator, kept in inventory, dispensed to subjects, returned by subjects, and returned to the Sponsor.
b. Return test articles as instructed upon completion or termination of the clinical study, or at the Sponsor's request.

**11. Study Records***

Maintain adequate and accurate records of all clinical study data, which are generally more exact and complete than those kept in ordinary medical practice.

a. Keep study records and source documents until the Sponsor has provided written approval for their destruction.
b. Ensure that data are recorded on source documents and transferred to the appropriate Case Report Forms for each study participant.
c. Adhere to Case Report Form Completion Guidelines provided by the Sponsor.

**12. Monitoring and Auditing**

Permit monitoring, auditing, and access to all study documents and make them available for inspection and copying by representatives of the Sponsor, the IRB/IEC, regulatory authorities, and other inspectors.

Notify the Sponsor of any written or verbal communication from a regulatory authority or inspector as soon as it occurs and work with the Sponsor to prepare a response to all such communication.

* Smith & Nephew, Inc. requires that all records relating to the conduct of this study be held by the Investigator for a period of at least 2 years following the approval of the test article or removal of the IND. If the Investigator retires, relocates, or for any other reason withdraws from responsibility of keeping the study records, custody must be transferred to the Sponsor or to a person who will accept responsibility and is approved by the Sponsor. Study records will not be destroyed without the written approval of the Sponsor.

### 13. HIPAA Authorization

For studies conducted in the US only, obtain written HIPAA authorization (or provide a waiver) for use and disclosure of protected health information (PHI) from each study participant (or legal representative) enrolled in the study using your current authorization form before performing any study-specific procedures on the study participant.

## 18.4 DECLARATION OF HELSINKI

This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice (GCP), effective for studies commencing after July 1996.