B. Braun Medical Inc.

FINAL CLINICAL STUDY PROTOCOL

Protocol Number: OPM-G-H-1506

Amendment 2

A Prospective Study of Quality of Life in Patients with Chronic Leg Wound(s) Treated with Prontosan® Wound Irrigation Solution and Prontosan® Wound Gel

Name of Products:	Prontosan® Wound Irrigation Solution and Prontosan® Wound Gel
Device Classification:	Unclassified
Phase of Development:	4 (post-marketing device study)
Study Indication:	Chronic leg wounds
Sponsor Contact:	Christopher R. Curtin Associate Manager, Medical Affairs B. Braun Medical Inc. 901 Marcon Blvd. Allentown, PA 18109 Tel: +1 610-596-2726 Fax: +1 610-849-1065
Protocol Version:	3.0
Protocol Date:	14 November 2018

SPONSOR APPROVAL PAGE

Wes Cetnarowski, MD
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and Chief Medical Officer

Date: 11/15/18

Angela Karpf, MD
Corporate Vice President, Medical Affairs

Date: _____

Rebecca Stolarick
Corporate Vice President, Regulatory Affairs

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Diana Valencia, MD
Associate Medical Director, Medical Affairs

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Associate Manager, Medical Affairs

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Senior Vice President, Scientific Affairs
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Corporate Vice President, Regulatory Affairs

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Diana Valencia, MD
Associate Medical Director, Medical Affairs
Date

14 Nov 18

Christopher R. Curtin
Associate Manager, Medical Affairs
Date:

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by B. Braun Medical Inc.
- Not to implement any changes to the protocol without written agreement from B. Braun Medical and prior review and written approval from the Institutional Review Board (IRB) except where necessary to eliminate an immediate hazard to patients.
- That I am thoroughly familiar with the appropriate use of the study device, as described in this protocol and any other information provided by B. Braun Medical.
- That I am aware of, and will comply with, good clinical practices (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the B. Braun Medical study device and of their study-related duties and functions as described in the protocol.

Signature: _____ Date: _____

Name (print): _____
Principal Investigator

Site Number: _____

CONTACT LIST

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Clinical Laboratory:	Local (site) laboratories will be used.

PROTOCOL AMENDMENTS

Original Protocol issued 22 March 2017
Amendments are listed beginning with the most recent amendment.

*In this summary document new text is **bolded** and **underlined** where as the deleted text is ~~struck through~~ for easy identification.*

Amendment 2: 14 November 2018

Amendment 2: Proposed List of Changes

The overall reason for the amendment: The overall reason for the amendment is to modify selected Inclusion/Exclusion criteria due to difficulties regarding subject recruitment.

Applicable Section(s)	Text Changes (new text in **bold/underlined**, deleted text in ~~strikeout~~)	Description of change / Rationale for Change
Throughout the document, minor typographical errors, misspellings and minor formatting issues have been resolved. These minor changes are not listed in this summary.		
Synopsis: Investigators/Study Sites:	~~Up to~~ **Approximately** 5 sites in the United States.	To allow additional sites if needed.
Synopsis: Inclusion Criteria; Section 7.1: Inclusion Criteria	Inclusion Criteria #3: At least one wound must have a surface area ≥5 cm^2 and ≤~~30~~ **50** cm^2 and it also must be present for ≥~~6~~ **4** weeks	Wound size increased after discussions with the Principal Investigators. Wound age decrease to 4 weeks which is the min age to be considered a chronic wound.
Appendix 2	To qualify for this study, the wound must be between 5 cm^2 and ~~30~~ **50** cm^2, inclusive.	
Synopsis: Exclusion Criteria;	Exclusion Criteria #4: Antibiotic therapy within ~~14~~ **7** days prior to baseline (i.e., prior to first administration of study treatment)……	Clarification on the restriction for the use of antibiotics.
Section 7.2: Exclusion Criteria	Exclusion Criteria #5: **Current** ~~Previous~~ diagnosis of **severe** peripheral artery disease **as indicated by clinical findings (i.e., no palpable pulse on both dorsal pedis and posterior tibial arteries of the affected limb) or**~~,~~ an Ankle Brachial Index of ≤ < 0.5~~7, and/or patient has no palpable pulse on both dorsal pedis and posterior tibial arteries of the affected limb~~	Clarification of the diagnosis of peripheral artery disease.
	Exclusion Criteria #7: Active **(flare up)** rheumatic or collagen vascular disease (including rheumatoid arthritis, scleroderma, and systemic lupus erythematosus), psoriasis, sarcoidosis, or other skin disease. **These subjects are allowed to receive oral, inhaled, or parenteral corticosteroids, immunosuppressive agents, or cytotoxic agents.**	Clarification to indicate the subject must be in an 'active' state of the disease and is permitted to take certain otherwise restricted medications.

	Note: fibromyalgia is acceptable. Exclusion Criteria #10: **Subjects with medical conditions other than those identified in Exclusion Criteria 7 who are currently** ~~Currently~~ receiving or has received oral, ~~inhaled,~~ or parenteral corticosteroids, immunosuppressive agents.....	Clarification of who is restricted from taking specified medications
Synopsis: Exclusion Criteria; Section 7.2: Exclusion Criteria	Exclusion Criteria #11: Clinical laboratory values that may impair wound healing; for example, ~~plasma total protein <4 g/dL,~~ hemoglobin <10 g/dL, or HbA1c ≥12% Exclusion Criteria #18: **Severe secondary** ~~l~~Lymphedema as diagnosed by clinical findings in inferior members (e.g., legs)	Plasma total protein restriction removed. This is not an accurate stand alone indicator of wound healing. Clarification on the type of lymphedema to be excluded.
Section 7.3: Withdrawal, Removal, and Replacement of Patients	Patient is administered any of the following prohibited therapies **after enrollment into the study**~~: any antibiotic therapy; oral, inhaled, or~~ parenteral corticosteroids, immunosuppressive agents, or cytotoxic agents **(see Exclusion Criteria #7 and Exclusion Criteria #10 for exceptions to this exclusion)**; or any **other** investigational drug or device **not utilized in this study**.	To be consistent with changes to Exclusion #7 and Exclusion #10
Section 8.3: Accountability and Compliance of Treatment	After accountability has been monitored for a completed or withdrawn patient, **previously dispensed** study product will be either **given to the subject,** returned to the Sponsor or destroyed on-site.	Subjects are permitted to keep previously dispensed Prontosan upon termination or completion of the study.
Section 8.4.2: Prior and Concomitant Medications	• ~~Oral or intravenous antibiotic therapy. Topical antibiotics not applied to the wound are acceptable.~~ **Any antibiotic therapy for treatment of the wound. Antibiotic therapy for treatment of infections not related to the wound are acceptable.** • Oral, ~~inhaled,~~ or parenteral corticosteroids, immunosuppressive agents, or cytotoxic agents **(see Exclusion Criteria #7 for exceptions)** .....At the re-screening, the patient must still meet all inclusion criteria and not exhibit any exclusion criteria, and the appropriate washout time for antibiotics (~~14~~7 days)	Use of non-wound related antibiotic therapy is permitted during the study. To be consistent with changes to Exclusion #4 and Exclusion #7
Section 10.3: Wound Measurement and Photography Appendix 2:	Wounds are to be measured using the clock method with the standard, single-use, disposable rulers ~~provided by the Sponsor~~.	Site are permitted to use their own disposable rulers.

Amendment 1: 31 May 2018

Amendment 1: Proposed List of Changes

The overall reason for the amendment: The overall reason for the amendment is to modify selected Inclusion/Exclusion criteria due to difficulties regarding subject recruitment.

Applicable Section(s)	Text Changes (new text in **bold/underlined**, deleted text in ~~strikeout~~)	Description of change / Rationale for Change
Throughout the document, minor typographical errors, misspellings and minor formatting issues have been resolved. These minor changes are not listed in this summary.		
Sponsor Approval	Diana Valencia, MD, Medical Affairs	B. Braun personnel and contact information update.
Contact List	~~Angela Karpf~~ **Diana Valencia** ~~Corporate Vice President~~ **Associate Director** Telephone: +1 610-596-~~2642~~**2875** Email: ~~angela.karpf~~**diana.valencia**@bbraun**usa**.com Christopher R. Curtin Email: chris.curtin@bbraun**usa**.com Sean D. Kennedy, MPH Email: ~~sean.kennedy@inventivhealth.com~~ **sean.kennedy@syneoshealth.com**	B. Braun and Syneos personnel and contact information updates.
Synopsis: Study Design, Week 1 (Baseline) Visit Section 6.1: Description of Overall Study Design and Plan Section 9.2.1: Week 0 (Screening) Section 9.2.2: Week 1 (Baseline)	At ≤ 1 week **±1 day** after the screening.....	Clarification of duration between Screening and Baseline visits.

Synopsis: Inclusion Criteria; Section 7.1: Inclusion Criteria	Inclusion Criteria #3: At least one wound must have a surface area ≥~~10~~**5** cm^2 and ≤~~16~~**30** cm^2 and it must also be present for ≥~~12~~**6** weeks	Wound age and size changed after discussions with the Principal Investigators following 3 months of no subject recruitment.
Synopsis: Exclusion Criteria; Section 7.2: Exclusion Criteria	Exclusion Criteria #4: Antibiotic therapy within 14 days prior to baseline (i.e., prior to first administration of study treatment). **Topical antibiotics not applied to the wound are acceptable.**	Clarification on the use of topical antibiotics.
Section 8.4.2: Prior and Concomitant Medications	~~Any~~ **Oral or intravenous** antibiotic therapy. **Topical antibiotics not applied to the wound are acceptable.**	Clarification on the use of topical antibiotics.
Section 13.1: Study Materials	~~The~~ **In addition to the Study Products, the** Sponsor will also supply the following items for this study:	Clarification of items supplied by the Sponsor.
Appendix 2	To qualify for this study, the wound must be between **5**~~10~~ cm^2 and ~~16~~**30** cm^2, inclusive.	Wound age and size changed after discussions with the 3 active Principal Investigators following 3 months of no subject recruitment.

1 SYNOPSIS

Title of Study:	A Prospective Study of Quality of Life in Patients with Chronic Leg Wound(s) Treated with Prontosan® Wound Irrigation Solution and Prontosan® Wound Gel
Protocol Number:	OPM-G-H-1506
Investigators/Study Sites:	Approximately 5 sites in the United States.
Phase of Development:	4 (post-marketing device study)
Objectives:	**Primary Objective** The primary objective of this study is to assess the overall change in the quality of life (QoL) after 4 weeks of treatment with Prontosan® Wound Irrigation Solution (Prontosan solution) and Prontosan® Wound Gel (Prontosan gel) in patients with chronic leg wound(s). This will be determined by calculating the change from baseline in the global score of the Wound-QoL questionnaire. **Secondary Objective** The secondary objective is to assess the changes in the Body, Psyche, and Everyday Life subscores of the Wound-QoL questionnaire after 4 weeks of treatment with Prontosan solution and Prontosan gel. **Exploratory Objective** The exploratory objective is to assess the change in the appearance and size of the wound(s) by direct evaluation and photographic measurements after 4 weeks of treatment with Prontosan solution and Prontosan gel.
Study Design:	This prospective, open-label, single-arm study will evaluate the change from baseline in Wound-QoL after 4 weeks of treatment with Prontosan solution and Prontosan gel in adult patients with chronic leg wounds. The change in the appearance and size of the wound(s) will also be evaluated. Patients must be outpatients at the start of the study. Patients can have no more then 2 wounds below the knee(s). The Investigator or designee will apply Prontosan solution and Prontosan gel to the wound(s) at clinic visits, and patients will apply Prontosan solution and Prontosan gel themselves (or have them applied by a caregiver) at home. Study specific procedures will be performed on both wounds. **Week 0 (Screening) Visit** At the Week 0 (screening) visit, after providing informed consent, patients will be screened for eligibility via review/assessment of inclusion and exclusion criteria.

	Assessments will include the Wound-QoL questionnaire (to be completed before any other procedure), demographics, concomitant medication review, medical history, vital signs, physical examination, wound history, wound assessments, and wound size measurements. Clinical laboratory tests (hematology and serum chemistry, including glycated hemoglobin [HbA1c]) will be performed if results are not available from tests done within 1 month prior to screening. **Week 1 (Baseline) Visit** At 1 week ± 1 day after the screening visit, eligible patients will be enrolled at the Week 1 (baseline) visit. At this visit, inclusion/exclusion criteria and medical and wound history will be confirmed, and the following assessments will be performed for the wound(s): the Wound-QoL questionnaire (to be completed before any other procedure), concomitant medication review, wound assessments, wound size measurements and photography of the wound(s) prior to and after cleaning/debridement, and adverse event (AE) review. The wound(s) will be treated with Prontosan solution and Prontosan gel by the Investigator or designee per the institutional guidelines and the Prontosan Instructions for Use (IFU). Bottles of Prontosan solution and Prontosan gel will be dispensed in sufficient quantity for the patient's treatment regimen until the next visit (Week 2). The patient (and/or the patient's caregiver) will be trained to administer the treatment at home, and the patient (and/or the caregiver) will be given a diary and trained to record the date and time of each treatment and any reactions to treatment in the diary. Patients (and/or caregivers) will also be instructed to record the liquid level remaining after each use, and to return all used bottles and any unused bottles of study treatment at the next visit for product accountability. **Week 2** At the Week 2 visit, the following assessments will be performed at the clinic for the wound(s): the Wound-QoL questionnaire (to be completed before any other procedure), patient diary review, product accountability review, concomitant medication review, wound assessment, wound size measurement and photography of the wound prior to and after cleaning/debridement, and AE review. The wound(s) will be treated with Prontosan solution and Prontosan gel by the Investigator or designee per the institutional guidelines and the Prontosan IFU. Bottles of Prontosan solution and Prontosan gel will be dispensed in sufficient quantity for the patient's treatment regimen until the next clinic visit (Week 5). The

	patient (and/or the caregiver) will receive instructions on how to continue the study procedures at home during Weeks 3 and 4. The patient will be given a new diary and retrained to record the date and time of each treatment and any reactions to treatment in the diary. Patients (and/or caregivers) will also be reinstructed to record the liquid level remaining after each use, and to return all used bottles and any unused bottles of study treatment at the next visit for product accountability. Wound-QoL questionnaires will be provided for patients, and instructions will be provided about completing the questionnaires at home during Weeks 3 and 4 on specific dates (on the same day each week). **Weeks 3 and 4** At Weeks 3 and 4, there are no scheduled study related clinic visits. Patients will continue Prontosan treatment at home according to the study doctor's instructions and according to the training received at the Week 2 visit. The study site will call the patients to remind them to complete the Wound-QoL questionnaires on specific dates (on the same day each week) and that on these dates, the Wound-QoL questionnaire must be completed prior to study treatment or other study procedures. Once during each week, the study site will also inquire about any changes or additions to a patient's concomitant medications. **Week 5 (End of Treatment or Early Discontinuation) Visit** At the Week 5 visit (final visit: end of treatment or early discontinuation), the following assessments will be performed for the wound(s): the Wound-QoL questionnaire (to be completed before any other procedure), patient diary review, product accountability review, concomitant medication review, vital signs, blood collection for clinical laboratory tests (hematology and serum chemistry), brief physical examination, wound assessment, wound size measurement and photography of the wound prior to and after cleaning/debridement, and AE review. The wound(s) will be treated with Prontosan solution and Prontosan gel (last treatment) by the Investigator or designee per the institutional guidelines and the Prontosan IFU. **Safety Follow-up** Any AE that causes a patient to be prematurely discontinued from the study will be followed until it resolves or stabilizes. Also, an AE that is considered to be related to study treatment (an adverse device effect [ADE]) identified at or before the Week 5 visit or a serious or medically important AE identified at or before the Week 5 visit will be followed until it resolves or stabilizes.

Selection of Patients:	**Inclusion Criteria** 1. Male or female ≥18 years of age 2. Either 2 wounds on 1 leg or 1 wound on each leg or only 1 wound. Wound(s) must be located below the knee. 3. At least one wound must have a surface area ≥5 cm^2 and ≤50 cm^2 and it also must be present for ≥4 weeks 4. Mean global score ≥1.18 on the Wound-QoL questionnaire (this will be calculated by the electronic data capture [EDC] system at the time of screening to assess eligibility) 5. Willingness to wear an off-loading device if medically indicated (e.g., DH shoe or walker) **Exclusion Criteria** 1. Prior treatment with Prontosan solution or Prontosan gel on the wound(s) 2. Infection in the wound(s) 3. Cartilage exposure in the wound(s) 4. Antibiotic therapy within 7 days prior to baseline (i.e., prior to first administration of study treatment). Topical antibiotics not applied to the wound are acceptable. 5. Current diagnosis of severe peripheral artery disease as indicated by clinical findings (i.e., no palpable pulse on both dorsal pedis and posterior tibial arteries of the affected limb) or an Ankle Brachial Index of < 0.5 6. Presence of gangrene in the wound(s) or on the leg(s) 7. Active (flare up) rheumatic or collagen vascular disease (including rheumatoid arthritis, scleroderma, and systemic lupus erythematosus), psoriasis, sarcoidosis, or other skin disease. These subjects are allowed to receive oral, inhaled, or parenteral corticosteroids, immunosuppressive agents, or cytotoxic agents. Note: fibromyalgia is acceptable. 8. Osteomyelitis diagnosed by x-ray, bone biopsy, or other radiological procedure within 90 days prior to the screening visit 9. Active radiation therapy below the hip 10. Subjects with medical conditions other then those identified in Exclusion Criteria 7 who are currently receiving or has received oral, or parenteral corticosteroids, immunosuppressive agents, or cytotoxic agents within 30 days prior to baseline (i.e., prior to first administration of study treatment) or is anticipated to require such agents during the course of the study

	11. Clinical laboratory values that may impair wound healing; for example, hemoglobin <10 g/dL, or HbA1c ≥12% 12. Enrolled in any investigational drug or device study for any disease/indication within 30 days prior to the screening visit 13. Unable to comprehend or comply with study requirements, or inability to sign an informed consent form 14. Allergic to any of the components in Prontosan solution or Prontosan gel 15. Patients who, in the opinion of the Investigator, would not be suitable candidates for this study or have some impediment to their ability to heal 16. Preplanned surgery or procedures that would occur during the study (other than deemed minor and clinically non-significant by the Investigator) or that would interfere with the study 17. Phase 4 pressure ulcer as defined by full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage or bone in the ulcer. Slough and/or eschar may be visible 18. Severe secondary lymphedema as diagnosed by clinical findings in inferior members (e.g., legs) 19. A diagnosis of malnutrition as determined by either a low BMI (<18.5 kg/m^2), or on the combined finding of weight loss together with reduced BMI (age-specific) 20. Employee of the Investigator or study center, with direct involvement in the study or other studies under the direction of that Investigator or study center, as well as family members of the employees or the Investigator
Planned Sample Size:	A sample size of 52 patients will have 80% power to detect a change from baseline to Week 5 of at least 0.35 points in the Wound-QoL global score (e.g., a baseline mean Wound-QoL global score of 3.53 and a follow-up mean Wound-QoL global score of 3.18), assuming an estimated standard deviation (SD) of differences of 0.88, using a paired t-test with a 0.050 two-sided significance level. Patients who withdraw or are withdrawn before completion of the Week 2 assessments and the Week 3 Wound-QoL questionnaire will be replaced to ensure that at least 52 patients will complete the study.
Device Description:	Prontosan Wound Irrigation Solution is a clear, colorless liquid containing purified water, 0.1% undecylenamidopropyl betaine, 0.1% polyaminopropyl biguanide (polyhexanide

	[PHMB]), and sodium hydroxide for pH adjustment. In this study, the 350-mL squeeze bottle will be used. Prontosan Wound Gel is a clear, colorless gel containing glycerol, hydroxyethylcellulose, 0.1% undecylenamidopropyl betaine, 0.1% PHMB, and purified water; it is packaged in a 30-mL squeeze bottle. The frequency and method of Prontosan solution and Prontosan gel applications will be per the institutional guidelines and the Prontosan IFU for the individual patient wound(s).
Reference Device:	Not applicable
Treatment Duration:	Each patient will receive 4 weeks of study treatment.
Criteria for Evaluation:	Patient QoL will be evaluated from the global score and the subscores (Body, Psyche, Everyday Life) of the Wound-QoL questionnaire to be assessed at Week 0 (screening visit) for eligibility, and at Weeks 1 (baseline visit), 2, 3, 4, and 5 (end of treatment or early discontinuation visit). Wound size(s) will be measured with standard, single-use, disposable rulers at Week 0 (screening visit) for eligibility; and measured with standard, single-use, disposable rulers and documented with digital photography before and after study treatment at Weeks 1 (baseline visit), 2, and 5. At screening, the Investigator will assess wound history for the wound(s) (wound type, wound age, location, past complications, and current dressing change frequency). At all visits, the Investigator will assess the wound(s) appearance, granulation tissue, exudate, drainage, surrounding erythema and/or swelling, and any signs of infection. Safety will be evaluated from AEs, ADEs, and physical examinations.

Study Endpoints:	**Primary Endpoint** • Change from baseline to Week 5 in the global score of the Wound-QoL questionnaire **Secondary Endpoints** • Change from baseline to Week 5 in the Body subscore of the Wound-QoL questionnaire • Change from baseline to Week 5 in the Psyche subscore of the Wound-QoL questionnaire • Change from baseline to Week 5 in the Everyday Life subscore of the Wound-QoL questionnaire **Exploratory Endpoint** • Change from baseline to Week 5 in the appearance and size of the wound(s)
Statistical Methods and Planned Analyses:	All data will be summarized, and where necessary, data will also be listed. For continuous variables, data will be summarized with the number of patients (N), mean, SD, median, minimum, and maximum. For categorical variables, data will be tabulated with the number and proportion of patients for each category. All patients who receive at least 2 weeks of study treatment and complete the Week 3 Wound-QoL questionnaire will be included in the primary analysis population used for all analyses. Additional populations may be explored and will be detailed in the Statistical Analysis Plan. Patients who withdraw or are withdrawn before completion of the Week 2 assessments and the Week 3 Wound-QoL questionnaire will be replaced to ensure that at least 52 patients will complete the study. Patient disposition will be summarized in terms of the number of patients who enter the study, the number who discontinue early, the number who complete the study and the number who are included in each relevant subgroup or baseline category. Demographic and baseline information will be summarized in tables using descriptive statistics. **Clinical Outcome Analyses** The global score of the Wound-QoL questionnaire will be summarized and explored in several ways. The primary analysis will be a paired t-test analysis of the mean global score of the Wound-QoL questionnaire at baseline and after 4 weeks of treatment. The global score of the Wound-QoL questionnaire may also be categorized to describe the proportion of patients with particular scores on individual questions, such as those with no score of 3 or 4 given, or to

	split the possible results into categories. Secondary analyses include the changes from baseline in the subscores of the Wound-QoL questionnaire for the Body, Psyche, and Everyday Life QoL dimensions. Exploratory analysis includes the change from baseline in the appearance and size of the wound(s). All endpoints will be summarized using descriptive statistics. Subgroup analyses may be performed based on such things as the size of the wound(s), the duration of treatment application, and the type of wound(s). **Safety** Treatment-emergent AEs (TEAEs; events with onset dates on or after the start of the study treatment) will be included in incidence tables. Serious AEs (SAEs), AEs causing discontinuation, and ADEs will be tabulated. All AEs will be listed by patient. Clinical laboratory data, vital signs, physical examination results, wound history, and medical history will be listed by patient. Listings and summary tables will be provided for prior medications and for concomitant medications initiated or continued during the study period. Study treatment exposure will be listed by patient and summarized descriptively.

2 TABLE OF CONTENTS

IN-TEXT TABLES

3 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
CFR	Code of Federal Regulations
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good clinical practice
HbA1c	Glycated hemoglobin
HIPAA	Health Insurance Portability Accountability Act
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
PHMB	Polyaminopropyl biguanide (polyhexanide)
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TIME	Tissue, Infection/Inflammation, Moisture, Edge

4 INTRODUCTION

4.1 Background on Chronic Leg Wounds

Chronic leg wounds are those that do not progress through the normal healing process in a timely manner. In the United States alone, these wounds are estimated to affect between 2.4 to 4.5 million patients.[1] Chronic wounds are typically classified as vascular ulcers (venous and arterial ulcers), diabetic ulcers, and pressure ulcers. As these wounds last on average 12 to 13 months and recur in up to 60% to 70% of patients, they can lead not only to a loss of function and a decreased quality of life, but also to an increase in morbidity. Primarily a condition of the elderly, chronic wounds are becoming more prevalent as populations age in developed countries and are associated with high treatment costs, estimated at 2% to 3% of the healthcare budgets in these countries.[2]

The physiological process of wound healing progresses through 4 main phases: hemostasis, inflammation, proliferation, and remodeling.[3] Immediately after an injury, vasoconstriction and blood clotting occurs, preventing blood loss and providing a provisional matrix for cell migration. Platelets secrete growth factors, and cytokines attract endothelial cells, fibroblasts, and immune cells. The inflammation stage usually lasts up to 7 days, during which time phagocytic cells are at work: neutrophils release reactive oxygen species and proteases that prevent bacterial contamination and cleanse the wound of cellular debris, and monocytes differentiate into tissue macrophages that remove bacteria and nonviable tissue and release growth factors and cytokines. As blood vessels are repaired and immune cells undergo apoptosis, the inflammation phase winds down and the proliferation phase begins. During the proliferation phase, tissue granulation, angiogenesis, and epithelialization occur. During the remodeling phase, which begins after the wound has closed and may last 1 to 2 years or longer, the provisional matrix is remodeled into organized collagen bundles.[3]

Chronic wounds often stall in the inflammation phase. Although they may differ in etiology, chronic wounds usually share some common features: elevated levels of proinflammatory cytokines, proteases, reactive oxygen species, and senescent cells; persistent infection; and a deficiency of stem cells and/or dysfunctional stem cells. Repeated tissue injury induces platelet-derived factors to stimulate the constant influx of immune cells; thus, the proinflammatory cytokine cascade becomes amplified and persists for a prolonged period, leading to elevated levels of proteases. Eventually, protease levels exceed the levels of their inhibitors, leading to the destruction of the extracellular matrix and the degradation of growth factors and their receptors. The destruction of the matrix not only prevents a progression to the proliferative phase, but also attracts more inflammatory cells, amplifying the inflammation cycle. Similarly, elevated levels of reactive oxygen species also damage the extracellular matrix, which stimulates proteases and inflammatory cytokines. This amplified inflammation cycle, together with the deficiency of functional stem cells, results in a failure to achieve complete re-epithelialization in tissue repair.[3,4]

In caring for chronic wounds, the concurrent management of both the underlying systemic problem (e.g., diabetes, peripheral arterial disease) and the wound bed preparation encourages the proper environment in which autolytic tissue repair can take place. The basic tenets of wound bed preparation have been described by the TIME acronym: Tissue assessment and management, Infection/Inflammation management, Moisture imbalance

management, and Edge of wound observation and management.[3] For tissue management, repetitive and maintenance debridement and wound cleaning are recognized as essential throughout the healing period. As almost all chronic wounds are thought to contain biofilms, topical antiseptics are commonly used to control bioburden in wounds. Excessive or insufficient wound exudate can be addressed with a wide range of dressings to regulate moisture balance, to protect peri-wound skin, and to optimize healing. At the edge of the wound, therapies such as negative pressure wound therapy may be used to help improve epithelial advancement and wound closure.[5]

Topically applied agents available for debridement, cleaning, and moistening acute and chronic wounds include such solutions as sterile saline, honey, povidone-iodine, cadexomer iodine, hypochlorous acid, a "super-oxidized" solution (sodium chloride/ sodium hypochlorite/ hypochlorous acid solution), collagenase, and polyhexamethylene biguanide [PHMB] (Prontosan® Wound Irrigation Solution and Prontosan® Wound Gel).[3,6]

4.2 Prontosan Wound Irrigation Solution and Prontosan Wound Gel

Prontosan Wound Irrigation Solution (Prontosan solution), manufactured for B. Braun Medical Inc. (the Sponsor), is a clear, colorless liquid containing purified water, 0.1% undecylenamidopropyl betaine as a surfactant, 0.1% polyaminopropyl biguanide (polyhexanide [PHMB]) as a preservative, and sodium hydroxide for pH adjustment.[9] Prontosan solution is an FDA (Food and Drug Administration)-cleared device indicated for cleaning wounds and for moistening and lubricating absorbent wound dressings for cuts, lacerations, ulcers, burns, post-surgical wounds, and abrasions.[7,8]

Prontosan Wound Gel (Prontosan gel), manufactured for B. Braun Medical Inc. (the Sponsor), is a clear, colorless gel containing glycerol, hydroxyethylcellulose, 0.1% undecylenamidopropyl betaine, 0.1% PHMB, and purified water.[10] Prontosan gel is an FDA-cleared device indicated for cleansing and moistening the wound bed and for the management of cuts, abrasions, lacerations, ulcers, first and second degree burns, partial and full thickness wounds, and surgical incisions. It can be used during wound dressing changes to soften encrusted wound dressings.[18,19]

Prontosan solution and Prontosan gel can also be used for cleansing and moistening chronic skin wounds.[9,10]

4.3 Clinical Risks/Benefits of Prontosan Solution and Prontosan Gel

According to the Prontosan solution and Prontosan gel Instructions for Use (IFU), in rare cases after application, a mild burning sensation has been observed, which subsided after a few minutes. Prontosan solution and Prontosan gel can cause allergic reactions such as itching and rashes. In <1:10,000 cases, anaphylactic shock has been reported.[9,10]

The following 3 studies demonstrated the clinical benefits of Prontosan solution and/or Prontosan gel: a prospective study of treating venous leg ulcers with Prontosan solution compared to saline solution, a retrospective study of treating venous leg ulcers with Prontosan solution compared to either Ringer's solution or normal saline solution, and a retrospective study of treating chronic wounds with Prontosan solution and Prontosan gel as a standard of care in a German hospital.[6,11,12]

A prospective, single-blind, randomized, controlled trial was done to examine the effects of Prontosan solution compared to saline solution in venous leg ulcers by means of clinical and instrumental assessments. Forty adult patients (22 females and 18 males between 55 and 73 years old) with painful, chronic leg ulcers >8 weeks old were randomized to 2 groups: 20 patients were treated every other day with Prontosan solution with standard wound care for 4 weeks, and 20 patients were treated every other day with saline solution with standard wound care for 4 weeks. A portable device was used on the wound bed to assess surface pH, which has been shown to correlate with the level of bacterial burden in different types of chronic wounds. Median baseline pH on the wound surface was 8.9; after 4 weeks of cleansing treatment and moist wound dressing, the median pH was reduced to 7.0 in the Prontosan group, which was statistically significantly lower than in the saline group ($p<0.05$). After 4 weeks, pain control (as measured on a visual analog scale) was statistically significantly better in the Prontosan group than in the saline group ($p<0.05$). Wound size was not significantly different in the 2 groups from baseline to the end of treatment, possibly due to the short study period. Prontosan solution was well tolerated by the patients.[6]

In a retrospective study of 110 patients with venous leg ulcers to examine clinical efficacy and cost-effectiveness, 57 patients were treated with Prontosan solution, and 53 were treated with Ringer's solution or normal saline solution. The wounds of the patients treated with Prontosan solution healed faster and in more cases (97% versus 89%). The Kaplan-Meier mean estimate (and associated standard error [SE]) demonstrated a statistically significant difference between groups ($p<0.0001$) in time to healing. The mean time to healing in the Prontosan group was 3.31 months (SE=0.17) compared to 4.42 months (SE=0.19) in the Ringer's/saline group. Thus, with faster healing, using Prontosan solution was considered cost-effective.[11]

A retrospective study was performed to assess the healing process of chronic and poorly healing wounds after the introduction of Prontosan solution and Prontosan gel to the standard of care at a municipal hospital in Germany (Municipal Hospital Bielefeld Mitte). The interventions added to the standard of care were routine irrigation of the wound with the irrigation solution at every dressing change and the additional application of the gel to every wound if there was no or only moderate exudate. The charts of 953 patients were analyzed 2 years after these changes were implemented. A total of 97% of patients had improved healing, with wound closure in 80% of these patients. Approximately two-thirds of patients found a great-to-complete reduction (improvement) in odor. In 29/953 (3%), a first or renewed wound infection developed after the beginning of treatment. A total of 99% had no pain or discomfort with Prontosan treatments; 1% experienced a slight burning sensation. On the basis of this analysis, the hospital continued the interventions as standard of care.[12]

4.4 Rationale

Improving health-related quality of life (QoL) is recognized as an important outcome measure for an intervention, especially for patients living with chronic conditions. In patients with chronic wounds, the physical symptoms of these wounds, especially pain, can dominate everyday living, affecting mobility, causing sleep disruption, and affecting work and social activities. In addition, having a chronic wound has been documented as causing frustration and anxiety.[13] The Wound-QoL questionnaire is a validated instrument for measuring the health-related QoL of patients with chronic wounds and for showing

measurable changes with interventions. With 17 items for patients to indicate the impact of their wounds on their activities and thoughts, the Wound-QoL questionnaire yields a global score to describe the overall impact and 3 subscores (Body, Psyche, and Everyday Life) to capture the specific QoL issues that contribute to this impact.[14] The Wound-QoL questionnaire is intended to be completed at 7-day intervals.

In this study, the Wound-QoL questionnaire will be used to assess patient QoL at baseline and after each week of treatment with Prontosan solution and Prontosan gel, with the primary endpoint being the change from baseline to Week 5 (final treatment visit) in global score. The Wound-QoL subscores of Body, Psyche, and Everyday Life will also be assessed. In addition to the QoL outcomes, the change from baseline in the appearance and size of the wound(s) will be examined.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Primary Objective

The primary objective of this study is to assess the overall change in the QoL after 4 weeks of treatment with Prontosan solution and Prontosan gel in patients with chronic leg wound(s). This will be determined by calculating the change from baseline in the global score of the Wound-QoL questionnaire.

5.1.2 Secondary Objective

The secondary objective is to assess the changes in the Body, Psyche, and Everyday Life subscores of the Wound-QoL questionnaire after 4 weeks of treatment with Prontosan solution and Prontosan gel.

5.1.3 Exploratory Objective

The exploratory objective is to assess the change in the appearance and size of the wound(s) by direct evaluation and photographic measurements after 4 weeks of treatment with Prontosan solution and Prontosan gel.

5.2 Study Endpoints

5.2.1 Primary Endpoint

The primary endpoint of this study is the change from baseline to Week 5 in the global score of the Wound-QoL questionnaire.

5.2.2 Secondary Endpoints

The secondary endpoints are as follows:

- Change from baseline to Week 5 in the Body subscore of the Wound-QoL questionnaire
- Change from baseline to Week 5 in the Psyche subscore of the Wound-QoL questionnaire

- Change from baseline to Week 5 in the Everyday Life subscore of the Wound-QoL questionnaire

5.2.3 Exploratory Endpoint

The exploratory endpoint is as follows:

- Change from baseline to Week 5 in the appearance and size of the wound(s)

6 INVESTIGATIONAL PLAN

6.1 Description of Overall Study Design and Plan

This prospective, open-label, single-arm study will evaluate the change from baseline in QoL after 4 weeks of treatment with Prontosan solution and Prontosan gel in adult patients with chronic leg wound(s). The change in the appearance and size of the wound(s) will also be evaluated.

Patients must be outpatients at the start of the study. Patients can have no more then 2 chronic wounds below the knee(s). The Investigator or designee will apply Prontosan solution and Prontosan gel to the wound(s) at clinic visits, and patients will apply Prontosan solution and Prontosan gel themselves (or have them applied by a caregiver) at home. Study specific procedures will be performed on both wounds.

Week 0 (Screening) Visit

At the Week 0 (screening) visit, after providing informed consent, patients will be screened for eligibility via review/assessment of inclusion and exclusion criteria. Assessments will include the Wound-QoL questionnaire (to be completed before any other procedure), demographics, concomitant medication review, medical history, vital signs, physical examination, wound history, wound assessments, and wound size measurements. Clinical laboratory tests (hematology and serum chemistry, including glycated hemoglobin [HbA1c]) will be performed if results are not available from tests done within 1 month prior to screening.

Week 1 (Baseline) Visit

At 1 week ± 1 day after the screening visit, eligible patients will be enrolled at the Week 1 (baseline) visit.

At this visit, inclusion/exclusion criteria and medical and wound history will be confirmed, and the following assessments will be performed for the wound(s): the Wound-QoL questionnaire (to be completed before any other procedure), concomitant medication review, wound assessment, wound size measurement and photography of the wound prior to and after cleaning/debridement, and adverse event (AE) review. The wound(s) will be treated with Prontosan solution and Prontosan gel by the Investigator or designee per the institutional guidelines and the Prontosan IFU. Bottles of Prontosan solution and Prontosan gel will be dispensed in sufficient quantity for the patient's treatment regimen until the next visit (Week 2). The patient (and/or the patient's caregiver) will be trained to administer the treatment at home, and the patient will be given a diary and trained to record the date and time of each treatment and any reactions to treatment in the diary. Patients (and/or caregivers) will also be instructed to record the liquid level remaining after each use, and to

return all used bottles and any unused bottles of study treatment at the next visit for product accountability.

Week 2

At the Week 2 visit, the following assessments will be performed for the wound(s) at the clinic: the Wound-QoL questionnaire (to be completed before any other procedure), patient diary review, product accountability review, concomitant medication review, wound assessment, wound size measurement and photography of the wound prior to and after cleaning/debridement, and AE review. The wound(s) will be treated with Prontosan solution and Prontosan gel by the Investigator or designee per the institutional guidelines and the Prontosan IFU. Bottles of Prontosan solution and Prontosan gel will be dispensed in sufficient quantity for the patient's treatment regimen until the next clinic visit (Week 5). The patient (and/or the caregiver) will receive instructions on how to continue study procedures at home during Weeks 3 and 4. The patient will be given a new diary and retrained to record the date and time of each treatment and any reactions to treatment in the diary. Patients (and/or caregivers) will also be reinstructed to record the liquid level remaining after each use, and to return all used bottles and any unused bottles of study treatment at the next visit for product accountability. Wound-QoL questionnaires will be provided for patients, and instructions will be provided about completing the questionnaires at home during Weeks 3 and 4 on specific dates (on the same day each week).

Weeks 3 and 4

At Weeks 3 and 4, there are no scheduled study related clinic visits. Patients will continue Prontosan treatment at home according to the study doctor's instructions and according to the training received at the Week 2 visit. The study site will call the patients to remind them to complete the Wound-QoL questionnaires on specific dates (on the same day each week) and that on these dates, the Wound-QoL questionnaire must be completed prior to study treatment or other study procedures. Once during each week, the study site will also inquire about any changes or additions to a patient's concomitant medications.

Week 5 (End of Treatment or Early Discontinuation) Visit

At the Week 5 visit (final visit: end of treatment or early discontinuation), the following assessments will be performed for the wound(s): the Wound-QoL questionnaire (to be completed before any other procedure), patient diary review, product accountability review, concomitant medication review, vital signs, blood collection for clinical laboratory tests (hematology and serum chemistry), brief physical examination, wound assessment, wound size measurement and photography of the wound prior to and after cleaning/debridement, and AE review. The wound(s) will be treated with Prontosan solution and Prontosan gel (last treatment) by the Investigator or designee per the institutional guidelines and the Prontosan IFU.

Safety Follow-up

Any AE that causes a patient to be prematurely discontinued from the study will be followed until it resolves or stabilizes. Also, an AE that is considered to be related to study treatment (an adverse device effect [ADE]) identified at or before the Week 5 visit or a serious or medically important AE identified at or before the Week 5 visit will be followed until it resolves or stabilizes.

6.2 Discussion of Study Design

As the purpose of the study is to examine how a 4-week regimen with Prontosan solution and Prontosan gel may impact the patient QoL from baseline to the final treatment visit, an open-label, single-arm design was chosen. The Wound-QoL questionnaire was chosen because of its specificity to chronic wounds, its conciseness and ease of patient completion, and its subscales that may provide a look at specific changes in the patient's life. The 4-week treatment period selected for this study is based on the current wound care approach that suggests if improvements in healing with standard care are not observed in 4 weeks, then a reassessment of the underlying pathology and a consideration for advanced treatments should be undertaken.[3] In addition, in the randomized clinical study comparing Prontosan solution with saline solution in the treatment of chronic leg ulcers, pain control (as measured on a visual analog scale) was statistically significantly better in the Prontosan group than in the saline group ($p<0.05$) after 4 weeks of treatment.[6] Thus, measureable changes in the patient QoL may be observed over this time period.

Using the same questionnaire; standard, single-use, disposable rulers; the same wound-measuring method; identical cameras; and the same photographic guidelines should ensure consistency across sites and over the period of the study. Training the patient and/or the caregiver in the institutional standard of treatment for home treatments and training the patient/caregiver to use the diary to record treatments should encourage compliance and consistency.

7 SELECTION AND WITHDRAWAL OF PATIENTS

7.1 Inclusion Criteria

Patients must meet all of the following criteria in order to be included in the study:

1. Male or female ≥18 years of age
2. Either 2 wounds on 1 leg or 1 wound on each leg or only 1 wound. Wound(s) must be located below the knee
3. At least one wound must have a surface area ≥5 cm^2 and ≤50 cm^2 and it must also be present for ≥4 weeks
4. Mean global score ≥1.18 on the Wound-QoL questionnaire (this will be calculated by the electronic data capture [EDC] system at the time of screening to assess eligibility)
5. Willingness to wear an off-loading device if medically indicated (e.g., DH shoe or walker)

7.2 Exclusion Criteria

Patients meeting any of the following criteria are ineligible to participate in this study:

1. Prior treatment with Prontosan solution or Prontosan gel on the wound(s)
2. Infection in the wound(s)
3. Cartilage exposure in the wound(s)

4. Antibiotic therapy within 7 days prior to baseline (i.e., prior to first administration of study treatment). Topical antibiotics not applied to the wound are acceptable.
5. Current diagnosis of severe peripheral artery disease as indicated by clinical findings (i.e., no palpable pulse on both dorsal pedis and posterior tibial arteries of the affected limb) or an Ankle Brachial Index of ≤ 0.5
6. Presence of gangrene in the wound(s) or on the leg(s)
7. Active (flare up) rheumatic or collagen vascular disease (including rheumatoid arthritis, scleroderma, and systemic lupus erythematosus), psoriasis, sarcoidosis, or other skin disease. These subjects are allowed to receive oral, inhaled, or parenteral corticosteroids, immunosuppressive agents, or cytotoxic agents. Note: fibromyalgia is acceptable.
8. Osteomyelitis diagnosed by x-ray, bone biopsy, or other radiological procedure within 90 days prior to the screening visit
9. Active radiation therapy below the hip
10. Subjects with medical conditions other than those identified in Exclusion Criteria 7 who are currently receiving or has received oral, or parenteral corticosteroids, immunosuppressive agents, or cytotoxic agents within 30 days prior to baseline (i.e., prior to first administration of study treatment) or is anticipated to require such agents during the course of the study
11. Clinical laboratory values that may impair wound healing; for example, hemoglobin <10 g/dL, or HbA1c $\geq$12%
12. Enrolled in any investigational drug or device study for any disease/indication within 30 days prior to the screening visit
13. Unable to comprehend or comply with study requirements, or inability to sign an informed consent form (ICF)
14. Allergic to any of the components in Prontosan solution or Prontosan gel
15. Patients who, in the opinion of the Investigator, would not be suitable candidates for this study or have some impediment to their ability to heal
16. Preplanned surgery or procedures that would occur during the study (other than deemed minor and clinically non-significant by the Investigator) or that would interfere with the study
17. Phase 4 pressure ulcer as defined by full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage or bone in the ulcer. Slough and/or eschar may be visible
18. Severe secondary lymphedema as diagnosed by clinical findings in inferior members (e.g., legs)
19. A diagnosis of malnutrition as determined by either a low BMI (<18.5 kg/m^2), or on the combined finding of weight loss together with reduced BMI (age-specific)

20. Employee of the Investigator or study center, with direct involvement in the study or other studies under the direction of that Investigator or study center, as well as family members of the employees or the Investigator

7.3 Withdrawal, Removal, and Replacement of Patients

A patient may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Unacceptable toxicity or AE
- Patient withdrawal of consent: At any time, a patient's participation in the study may terminate at his/her request. The reason for patient withdrawal will be noted in the electronic case report form (eCRF).
- Intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that becomes apparent during treatment and necessitates the patient's termination from the study.
- General or specific changes in the patient's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria.
- Protocol deviation: The patient's findings or conduct fail to meet the protocol entry criteria or fail to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The deviation may necessitate premature termination from the study.
- Patient is administered any of the following prohibited therapies after enrollment into the study: parenteral corticosteroids, immunosuppressive agents, or cytotoxic agents (see Exclusion Criteria #7 and Exclusion Criteria #10 for exceptions to this exclusion); or any other investigational drug or device not utilized in this study.
- Lost to follow-up: The patient stops coming for visits, and study personnel are unable to contact the patient.
- Patient discontinuation on the basis of the Investigator's clinical judgment.
- This study may be terminated at the discretion of the Sponsor or any regulatory agency. An Investigator may elect to discontinue or stop the study at his or her site for any reason including safety or low enrollment.

Patients who withdraw or are withdrawn before completion of the Week 2 assessments and the Week 3 Wound-QoL questionnaire will be replaced to ensure that at least 52 patients will complete the study.

7.4 Follow-Up for Patient Withdrawal from Study

If a patient discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the medical monitor. The date and the reason for study discontinuation must be recorded on the eCRF. Patients who withdraw prematurely are to attend an early discontinuation visit, if possible, and complete all assessments.

In the event that a patient discontinues prematurely from the study due to a treatment-emergent AE (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to be no longer clinically significant.

Once a patient is withdrawn from the study, the patient may not re-enter the study. Patients who withdraw or are withdrawn before completion of the Week 2 assessments and the Week 3 Wound-QoL questionnaire will be replaced to ensure that at least 52 patients will complete the study.

8 TREATMENTS

8.1 Details of Study Product

Prontosan Wound Irrigation Solution is a clear, colorless liquid containing purified water, 0.1% undecylenamidopropyl betaine as a surfactant, 0.1% polyaminopropyl biguanide (polyhexanide [PHMB]) as a preservative, and sodium hydroxide for pH adjustment. The device is cleared by the FDA for prescription and over-the-counter use for cleaning wounds and for moistening and lubricating absorbent wound dressings for the management of cuts, lacerations, ulcers, burns, post-surgical wounds, and abrasions.[7,8]

Prontosan Wound Gel is a clear, colorless gel containing glycerol, hydroxyethylcellulose, 0.1% undecylenamidopropyl betaine, 0.1% PHMB, and purified water. The device is cleared by the FDA for prescription and over-the-counter use for cleaning and moistening the wound bed and for the management of cuts, abrasions, lacerations, ulcers, first- and second-degree burns, partial and full thickness wounds, and surgical incisions. It can be used during wound dressing changes to soften encrusted wound dressings.[18,19]

Commercially available Prontosan solution and commercially available Prontosan gel will be provided by the Sponsor for the study. Prontosan solution will be provided in 350-mL bottles and packed in cartons containing up to 10 bottles. Prontosan gel will be provided in 30-mL bottles and packed in cartons containing up to 20 bottles. Each carton will be labeled with the name and address of the Sponsor, the lot number, the expiration date, and will contain the product usage instructions. Cartons will be distributed to the study sites.

Storage

Prontosan solution and Prontosan gel are to be stored under controlled room temperature. Controlled room temperature is defined by the United States Pharmacopeia (USP) as 20 to 25°C (68 to 77°F) with allowed excursions between 15 to 30°C (59 to 86°F). Avoid storing these products in excessive heat, and do not refrigerate or freeze these products.

Use Prontosan solution and Prontosan gel prior to the expiration dates noted on the package labels. Prior to opening the bottle, the product is sterile by aseptic filtration (<1 CRU/mL), and the fluid and fluid path is nonpyrogenic prior to removal of the cap.

Each bottle is for single-patient use only. There is a shelf-life of 28 days after opening a bottle of Prontosan solution or Prontosan gel as long as the bottle is closed immediately after use, and the top of the bottle is protected from contamination or direct contact. Be sure to record the date opened on the designated space on the bottles.

Warnings

Prontosan solution and Prontosan gel are for external use only. Do not use for infusion or injection, and do not ingest.

Contraindications include the following: do not use on patients with a history of allergy to any of the ingredients, do not use in the presence of hyaline cartilage, and do not use in combination with anionic tensides (as these may impair preservation). Also, when removing soaps, lotions, ointments, oils, or enzymes from the wound, ensure that the entire wound is thoroughly rinsed with Prontosan solution.

8.2 Dosage Schedule

The frequency and method of application will be per the institutional guidelines and the Prontosan IFU for the individual patient wound(s). Prontosan solution and Prontosan gel are to be used according to these guidelines during the 4-week treatment period. Prontosan solution will be used to rinse and clean the wound(s) and the surrounding area; bandages or dressings may be soaked in the solution and/or the gel and used for cleaning as required. After the wound(s) has/have been cleaned (and in the clinic, measured and photographed), Prontosan gel will be applied directly as a 3-5 mm coating on shallow flat wound surfaces or deep wound fissures. Bandages or dressings will then be applied per institutional guidelines and Prontosan IFU.[9,10]

When patients are at a clinic visit, the Investigator or designee will administer study treatment. At Weeks 1 and 2, the Investigator or designee will dispense enough Prontosan solution and Prontosan gel for the patient's treatment until the next study visit. The patient (and/or the patient's caregiver) will be trained to administer the treatment at home, and the patient will be given a diary and trained to record the date and time of each treatment and any reactions to treatment. Patients (and/or caregivers) will also be instructed to record the liquid level remaining after each use, and to return all used bottles and any unused bottles of study treatment at the next visit for product accountability.

8.3 Accountability and Compliance of Treatment

The Investigator or designee will maintain records of Prontosan solution and Prontosan gel delivered to the study site, the inventory at the site, the distribution to and use by each patient, and if approved, the on-site destruction of used and unused Prontosan solution and gel, or the return of materials to the Sponsor for storage or disposal. These records may include dates, quantities, lot numbers, expiration dates, and in-clinic temperature log.

Administration of study treatment in the clinic will be performed by the Investigator or designee, ensuring compliance with the individual patient's regimen.

At each visit after initiation of treatment, site staff will record compliance of patients with their assigned regimen. Patients will be instructed to bring their diaries and Prontosan bottles (used and unused bottles) back for inspection at each study visit. Patients are to be reminded of the importance of compliance with their assigned regimen, with an emphasis on administering their study treatment as they were instructed and staying on the schedule they were given for their wound care.

Used bottles and unused bottles must be returned at each visit, as compliance will be assessed by bottle usage. The Investigator or designee will record in the eCRF (yes/no) if the products were used correctly. Discontinuation for noncompliance is at the Investigator's discretion.

After accountability has been monitored for a completed or withdrawn patient, previously dispensed study product will be either given to the subject, returned to the Sponsor or destroyed on-site.

8.4 Medical History and Prior and Concomitant Medications

8.4.1 Medical History

Investigators should document prior significant illnesses that the patient has experienced prior to signing the ICF; this is the patient's medical history. New illnesses present after the ICF is signed and up to the time of first treatment (Week 1) are to be regarded as concomitant illnesses. Illnesses first occurring or detected during or after the first administration of study treatment and/or worsening of a concomitant illness during or after the first administration of study treatment are to be documented as AEs in the eCRF.

8.4.2 Prior and Concomitant Medications

Any medication or therapy that is taken by or administered to the patient during the course of the study must be recorded in the eCRF. Prior medications are defined as those taken by or administered to the patient before screening and up to the first study treatment. Concomitant medications are defined as those taken by or administered to the patient after the first study treatment. After the first treatment, medication to treat minor treatment-emergent illness is generally permitted; however, the following therapies are expressly prohibited throughout the study:

- Any antibiotic therapy for treatment of the wound. Antibiotic therapy for treatment of infections not related to the wound are acceptable.
- Oral, or parenteral corticosteroids, immunosuppressive agents, or cytotoxic agents (see Exclusion Criteria #7 for exceptions)
- Any investigational drug or device
- Any additional wound treatment topical solutions, including medicated dressings

At screening, if a patient has a wound infection that is being treated with one of these prohibited medications, the patient may be scheduled for a re-screening after the infection in the wound has cleared. At the re-screening, the patient must still meet all inclusion criteria and not exhibit any exclusion criteria, and the appropriate washout time for antibiotics (7 days) and/or for corticosteroids, immunosuppressive agents, and cytotoxic agents (30 days) must have been met prior to the first study treatment.

During the study, if a patient develops an infection in the wound(s) and requires treatment with a prohibited medication, the patient will be discontinued from the study. Patients who withdraw or are withdrawn before completion of the Week 2 assessments and the Week 3 Wound-QoL questionnaire will be replaced to ensure that at least 52 patients will complete the study.

9 STUDY PROCEDURES

Table 1 outlines the timing of assessments to be performed throughout the study. See Sections 10 and 11 for additional details of study procedures.

Table 1 Schedule of Assessments

Period	Screening Visit	Treatment Period				
		Baseline Visit				Final Visit (End of Treatment)[a]
Week	Week 0	Week 1 (1 week ±1 day after screening)	Week 2 (±1 day)	Week 3 (±1 day)	Week 4 (±1 day)	Week 5 (±1 day)
Visit	1	2	3	At home	At home	4
Informed Consent	X					
Demographics	X					
Inclusion/Exclusion Criteria	X	X				
Medical History/ Wound History	X	X				
Concomitant Medication Review	X	X	X	X	X	X
Vital Signs[b]	X					X
Physical Examination	X					
Brief Physical Examination						X
Collect Blood for Clinical Laboratory Tests	X[c]					X
Wound-QoL Questionnaire[d]	X	X	X	X	X	X
Wound Assessment[e]	X	X	X			X
Measure Wound(s) Size Using Study Rulers	X	X[f]	X[f]			X[f]
Photograph Wound(s) Using Study Camera		X[f]	X[f]			X[f]
Dispense Diary[g]		X	X			
Collect/Review Diary			X			X
Administer Study Treatment [h]		X	X	X	X	X
Provide/Review Instructions on Treatment and Diary[g]		X	X			
Dispense Study Treatment[g]		X	X			
Perform Study Treatment Accountability			X			X

Period	Screening Visit	Treatment Period				
		Baseline Visit				Final Visit (End of Treatment)[a]
Week	Week 0	Week 1 (1 week ±1 day after screening)	Week 2 (±1 day)	Week 3 (±1 day)	Week 4 (±1 day)	Week 5 (±1 day)
Visit	1	2	3	At home	At home	4
Adverse Event Assessment[i]		X	X	X	X	X

Abbreviations: AE=adverse event; IFU=Instructions for Use; Wound-QoL=Wound Quality of Life

[a]Or early discontinuation visit.

[b]Vital sign measurements will be performed at screening and at the Week 5 (end of treatment or early discontinuation) visit.

[c]At screening, clinical laboratory tests will be done only if results from tests performed within 1 month prior to screening are not available. Tests include standard hematology and serum chemistry, plus glycated hemoglobin.

[d]Patients must complete the Wound-QoL questionnaire before any other study-related procedure, including any dressing change (with the exception of consenting the patient at screening). Patients will be given several blank Wound-QoL questionnaires at the Week 2 visit to fill out on specific dates during Weeks 3 and 4 (on the same day each week); study site personnel will call the patient on these dates to remind them to fill out the questionnaires prior to study treatment on those dates.

[e]The Investigator or designee will assess the wound(s) for appearance, granulation tissue, exudate, drainage, surrounding erythema and/or swelling, and any signs of infection.

[f]To be done pre-cleaning and post-cleaning.

[g]A diary and sufficient study treatment to use until the next visit will be dispensed to patients. Instructions on administering study treatment, recording treatment dates and times and any reactions to treatment in the diary will be explained to the patient and/or caregiver.

[h]Prontosan solution and Prontosan gel will be administered by the Investigator or designee at each clinic visit. At home, patients or their caregivers will administer Prontosan solution and Prontosan gel. Each patient's treatment regimen will be given per the institutional guidelines and the Prontosan IFU.

[i]At home, AEs are collected in the patient diary. In the clinic, patients are assessed for AEs by the Investigator.

9.1 Patient Informed Consent

The Investigator or designee will explain the nature of the study, the study procedures, and the potential risks to each patient. Before any study-related procedures occur, the patient must voluntarily sign the ICF.

9.2 Procedures by Study Week

Assessments are to be performed as outlined in the following by-week subsections. If the patient has 2 wounds, both wounds will be treated with the Prontosan Solution and Prontosan Gel and other study specific procedures will be performed on both wounds.

9.2.1 Week 0 (Screening)

The following assessments will be performed by the Investigator or designee at the screening visit (Week 0, Visit 1):

- Obtain informed consent.
- After the patient gives consent, ask the patient to complete the Wound-QoL questionnaire before any other visit assessment.
- Obtain demographic data.
- Collect medical history and wound history (including wound type, wound age, location, past complications, and current dressing change frequency) for both wounds if 2 are present.
- Record prior and concomitant medications for the wound(s) and other indications.
- Measure vital signs (blood pressure, pulse, temperature) and weight and height.
- Perform a physical examination.
- Assess the wound(s) appearance, granulation tissue, exudate, drainage, surrounding erythema and/or swelling, and any signs of infection.
- Measure the wound(s) size with a standard, single-use, disposable ruler using the clock method (see Section 10.3 and Section 15, Appendix 2).
- Collect blood for measuring HbA1c and for standard hematology and serum chemistry parameters if the results are not available for tests done within 1 month prior to screening.
- Review the inclusion/exclusion criteria to assess eligibility.

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to enter the study and will be assigned a patient number. Eligibility will be confirmed at the Week 1 visit (Baseline, Visit 2) which will occur 1 week ± 1 day after the Screening visit.

9.2.2 Week 1 (Baseline)

The Week 1 visit (baseline visit) will occur 1 week ± 1 day following the screening visit.

At the Week 1 visit, the following assessments will be performed by the Investigator or designee:

- Ask the patient to complete the Wound-QoL questionnaire before any other visit assessment.
- Confirm patient eligibility.
- Confirm medical and wound histories.
- Record concomitant medications.
- Assess the wound(s) appearance, granulation tissue, exudate, drainage, surrounding erythema and/or swelling, and any signs of infection.
- Measure the wound(s) size pre-treatment (pre-debridement) with a standard, single-use, disposable ruler using the clock method (see Section 10.3 and Section 15, Appendix 2).
- Photograph the wound(s) pre-treatment (pre-debridement) using the study camera and a standard, single-use, disposable ruler to indicate relative size.
- Clean the wound(s) and wound area(s) with Prontosan solution per the institutional guidelines and the Prontosan IFU for the individual patient wound(s).
- Assess the patient for any AEs.
- Measure the wound(s) size post-cleaning (post-debridement) with a standard, single-use, disposable ruler using the clock method.
- Photograph the wound(s) post-cleaning (post-debridement) using the study camera and a standard, single-use, disposable ruler to indicate relative size.
- Apply Prontosan gel to the wound(s) and apply the bandage/dressing per the institutional guidelines and the Prontosan IFU for the individual patient wound(s).
- Dispense enough study treatment to the patient to last until the next study visit.
- Provide training to the patient (and/or the caregiver) on administering the study treatment at home.
- Instruct the patient (and/or the caregiver) to record the liquid level remaining after each use, and to return all used bottles and any unused bottles of study treatment at the next visit for product accountability.
- Dispense a diary to the patient and provide training to the patient (and/or the caregiver) to record the date and time of each treatment and any reactions to treatment. Remind the patient to bring the diary to the next visit.

9.2.3 Week 2

At the Week 2 visit, the following assessments will be performed by the Investigator or designee:

- Ask the patient to complete the Wound-QoL questionnaire before any other visit assessment.
- Review the diary and examine used bottles and any unused bottles of study treatment.
- Record concomitant medications.
- Assess the wound(s) appearance, granulation tissue, exudate, drainage, surrounding erythema and/or swelling, and any signs of infection.

- Measure the wound(s) size pre-treatment (pre-debridement) with a standard, single-use, disposable ruler using the clock method (see Section 10.3 and Section 15, Appendix 2).
- Photograph the wound(s) pre-treatment (pre-debridement) using the study camera and a standard, single-use, disposable ruler to indicate relative size.
- Clean the wound(s) and wound area(s) with Prontosan solution per the institutional guidelines and the Prontosan IFU for the individual patient wound(s).
- Assess the patient for any AEs.
- Measure the wound(s) size post-cleaning (post-debridement) with a standard, single-use, disposable ruler using the clock method.
- Photograph the wound(s) post-cleaning (post-debridement) using the study camera and a standard, single-use, disposable ruler to indicate relative size.
- Apply Prontosan gel to the wound(s) and apply the bandage/dressing per the institutional guidelines and the Prontosan IFU for the individual patient wound(s).
- Dispense enough study treatment to the patient to last until the next study visit.
- Provide training to the patient (and/or the caregiver) on administering the study treatment at home.
- Instruct the patient (and/or the caregiver) to record the liquid level remaining after each use, and to return all used bottles and any unused bottles of study treatment at the next visit for product accountability.
- Dispense a new diary to the patient and provide training to the patient (and/or the caregiver) to record the date and time of each treatment and any reactions to treatment. Remind the patient to bring the diary to the next visit.
- Provide several blank Wound-QoL questionnaires to the patient and ask the patient to complete one of them on a specific date during Week 3 and another on a specific date during Week 4 (on the same day each week).

9.2.4 Weeks 3 and 4

During Weeks 3 and 4, patients will either self-administer study treatment or be treated by their caregiver (as trained by the Investigator or designee). Frequency of administration will vary by patient per the regimen provided by the Investigator or designee.

On dates specified by the study site (one during Week 3 and one during Week 4, on the same day each week), patients will complete the Wound-QoL questionnaire prior to any study treatments on those days. Site personnel will call patients to remind them to complete the questionnaires and to reinforce completing the diary at each treatment. Site personnel will also ask about any concomitant medication changes.

9.2.5 Week 5 (Final Visit: End of Treatment or Early Discontinuation)

At the Week 5 visit (final visit: end of treatment or early discontinuation), the following assessments will be performed by the Investigator or designee:

- Ask the patient to complete the Wound-QoL questionnaire before any other visit assessment.

- Review the diary and examine used bottles and any unused bottles of study treatment.
- Record concomitant medications.
- Measure vital signs (blood pressure, pulse, temperature).
- Collect blood for measuring HbA1c and for standard hematology and serum chemistry parameters.
- Perform a brief physical examination.
- Assess the wound(s) appearance, granulation tissue, exudate, drainage, surrounding erythema and/or swelling, and any signs of infection.
- Measure the wound(s) size pre-treatment (pre-debridement) with a standard, single-use, disposable ruler using the clock method (see Section 10.3 and Section 15, Appendix 2).
- Photograph the wound(s) pre-treatment (pre-debridement) using the study camera and a standard, single-use, disposable ruler to indicate relative size.
- Clean the wound(s) and wound area(s) with Prontosan solution per the institutional guidelines and Prontosan IFU for the individual patient wound(s).
- Assess the patient for any AEs.
- Measure the wound(s) size post-cleaning (post-debridement) with a standard, single-use, disposable ruler using the clock method.
- Photograph the wound(s) post-cleaning (post-debridement) using the study camera and a standard, single-use, disposable ruler to indicate relative size.
- Apply Prontosan gel to the wound(s) and apply the bandage/dressing per the institutional guidelines and the Prontosan IFU for the individual patient wound(s).

Patients who prematurely withdraw from the study for any reason should complete these early discontinuation visit requirements. If the early discontinuation visit is not done, the reason(s) will be recorded in the eCRF. Patients who withdraw or are withdrawn before completion of the Week 2 assessments and the Week 3 Wound-QoL questionnaire will be replaced to ensure that at least 52 patients will complete the study.

9.2.6 Unscheduled Visits

The Investigator may at his/her discretion arrange for a patient to have an unscheduled assessment, especially in the case of AEs or ADEs that require follow-up. The unscheduled visit page in the eCRF must be completed.

10 CLINICAL OUTCOME ASSESSMENTS

In this study, clinical outcome will be assessed by evaluating patient-reported QoL and Investigator-reported wound(s) size and assessments.

10.1 Wound Quality of Life Questionnaire

The Wound-QoL questionnaire measures the health-related QoL of patients with chronic wounds (see Section 15, Appendix 1). This short, validated questionnaire was developed based on the Freiburg Life Quality Assessment for wounds, the Cardiff Wound Impact Schedule, and the Wurzburg Wound Score.[13,15] The questionnaire is self-explanatory, and

patients fill it in themselves. The Investigator or designee should instruct patients to check off only 1 box per line, in a box (not between boxes), and to answer all questions. In this study, patients are to complete the questionnaire during each week (Weeks 0-5). This questionnaire should be the first task performed at each visit. After the patient completes the questionnaire, the Investigator or designee should check that the questionnaire was completed legibly and completely.

The questionnaire consists of 17 statements of impairments. The patient assesses and documents the degree to which the impairments affected him/her within the previous 7 days by ticking checkboxes using a Likert scale from 0 to 4: 0=not at all, 1=a little, 2=moderately, 3=quite a lot, 4=very much. The global score, an average of all 17 items, reflects 3 QoL dimensions—Body (5 items), Psyche (5 items), and Everyday Life (6 items)—plus 1 item about financial burden. Subscores on the Body, Psyche, and Everyday Life QoL dimensions are calculated by averaging the respective items in these subscales: the Body subscale consists of Items 1-5, the Psyche subscale consists of Items 6-10, and the Everyday Life subscale consists of Items 11-16. Item 17, the statement about financial burden, does not belong in any of the subscales.14,[15,16]

If more than 1 box is checked within an item, or if a patient has checked between 2 checkboxes, the item is treated as missing. Missing items are not averaged in the global score. A global score can be computed only if at least 75% of the items have been answered and are not treated as discarded or as missing (at least 13 of the 17 items are valid), and a subscore can be computed only if no more than 1 item of the subscale is missing.[14,15,16]

10.2 Wound Assessment

The subject may have 2 chronic wounds below 1 knee or 1 chronic wound below each knee or only 1 chronic wound below either knee.

At screening, the Investigator or designee will collect the wound history for the wound(s), including wound type, wound age, location, past complications, and current dressing change frequency.

At each visit, the Investigator or designee will assess the wound(s) in terms of the wound appearance, granulation tissue, exudate, drainage, surrounding erythema and/or swelling, and any signs of infection.

10.3 Wound Measurement and Photography

The size of the wound(s) will be measured at screening (Week 0), and pre-treatment (pre-debridement) and post-cleaning (post-debridement) at each subsequent visit (Weeks 1, 2, and 5), and the wound(s) will be photographed pre-treatment and post-cleaning at Weeks 1, 2, and 5. For consistency, whenever possible, the same evaluator at each site should perform the measurements and photography across visits.

Wounds are to be measured using the clock method with the standard, single-use, disposable rulers. With this technique, you will generate an imaginary box around the wound by measuring the longest length and the greatest width using the body orientation as an imaginary clock (12:00 is the head, and 6:00 is the feet).

Document all measurements in centimeters (cm) and calculate the surface area of the wound (length x width) in cm^2. Further details for using the clock method are presented in Section 15, Appendix 2.

Photographs are to be taken only with the digital camera provided to the site by the Sponsor. Specific camera instructions, along with general guidelines for preparing the patient and the room and for taking wound photographs, are described in the photography manual to be provided to the site.

11 SAFETY ASSESSMENTS

Safety assessments, including vital signs, physical examinations, AE and ADE review, and clinical laboratory tests, are to be performed at the visits specified in the schedule of assessments in Table 1.

11.1 Vital Signs

Vital signs (systolic and diastolic blood pressure measurements, pulse rate, and temperature) will be evaluated at screening and at the Week 5 (end of treatment or early discontinuation) visit. All vital signs will be measured after the patient has been resting in a sitting position for at least 5 minutes. Body weight and height will also be recorded (screening visit only).

Out-of-range blood pressure or pulse rate measurements will be repeated at the Investigator's discretion. Vital sign measurements will be repeated up to 2 times, with a rest of at least 5 minutes between readings. All clinically significant changes from baseline must be recorded as AEs.

11.2 Physical Examination

A complete physical examination (head, ears, eyes, nose, throat, heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems) will be performed at the screening visit. A brief physical examination will be performed at the Week 5 visit (end of treatment or early discontinuation). Physical examinations will be performed by the Investigator or other designated study physician. Medical history will be recorded at screening, and concomitant illnesses will be recorded up to the first treatment at Week 1. Wound history, recorded at screening and Week 1, will include wound type(s), wound age(s), location, past complications, and current dressing change frequency.

All clinically significant changes from baseline must be recorded as AEs.

11.3 Laboratory Assessments

Blood samples are to be obtained at screening for glycated hemoglobin and standard clinical laboratory assessments (Table 2) if results are not available for tests performed within 1 month prior to screening. At the Week 5 visit (end of treatment or early discontinuation), blood samples will be obtained for clinical laboratory assessments. The amount of blood obtained from each patient in this study should not exceed 30 mL. Blood samples will be analyzed at the local (site) laboratory.

Table 2 Clinical Laboratory Assessments

Hematology	Serum Chemistry
Full and differential blood count Hematocrit (Hct) Hemoglobin (Hb) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential Glycated hemoglobin (HbA1c).	Albumin Alanine aminotransferase (ALT) Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Blood urea nitrogen (BUN) or urea Carbon dioxide (CO_2) Creatinine Creatine kinase and subtypes Electrolytes (Na, K, Cl, Ca, P) Gamma-glutamyl transpeptidase (GGT) Glucose Lactate dehydrogenase (LDH) Total bilirubin Direct bilirubin

11.4 Adverse Events

11.4.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs.

Adverse device effects (ADEs) are defined as AEs that are considered related to the study device. Possible anticipated ADEs with Prontosan solution or Prontosan gel include burning sensation, itching, and rash. In rare cases (1:10,000), anaphylactic shock has been reported after use of Prontosan solution or Prontosan gel.[9,10]

Patients and/or caregivers will be instructed to report AEs in the diary, and patients will be monitored for AEs at each study visit. All AEs are to be followed until resolution or until a stable clinical endpoint is reached.

Each AE is to be documented in the eCRF with reference to start and stop dates, frequency, severity, relationship to study device (related: yes or no), action taken with study device, treatment of event, and outcome. Furthermore, each AE and each ADE are to be classified as being serious or non-serious. Changes in AEs and AE resolution dates are to be documented in the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the patient gives informed consent until the final visit. Follow-up of an AE, even

after the end of treatment, is required until the event resolves or stabilizes at a level acceptable to the Investigator.

Specific guidelines for classifying AEs by intensity are given in Table 3.

Table 3 Classification of Adverse Events by Intensity

Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe: An event that prevents normal everyday activities.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

11.4.2 Serious Adverse Events and Serious Adverse Device Effects

An AE is considered "serious" if in the view of either the Investigator or Sponsor, it meets 1 or more of the following criteria:

- Is fatal
- Is life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered serious AEs (SAEs) if they are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE.

A serious ADE is an ADE that has resulted in any of the consequences characteristic of an SAE.

11.4.3 Serious Adverse Event Reporting

An SAE occurring during the study must be reported to the Sponsor or designee (details for reporting will be in the Safety Plan and on the SAE form). Any such SAE due to any cause, whether or not related to the study device, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. Notification can be made with the SAE reporting form as described in the following paragraphs:

1. Contact the study safety team to inform them that you are faxing an SAE form. The study safety team is available 24 hours a day, 7 days a week. If you are unable to speak with a live safety associate, leave a message with the name of the Investigator, your name, the telephone number where you can be reached, and the protocol number and title.
2. Fax the SAE form and any supporting documentation to the study safety team within 24 hours of becoming aware of the event. Verify successful transmission by

obtaining a Fax Confirmation Report; this confirmation page should be kept with the SAE report in case future monitoring is required.

The event must also be recorded on the AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the Investigator considers the event to be related to the study device.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The Investigator must report all additional follow-up evaluations to the Sponsor Study Physician within 10 calendar days. All SAEs will be followed until the Investigator and Sponsor agree the event is satisfactorily resolved. The Sponsor will report SAEs to the FDA.

Suspected unexpected serious adverse reactions (SUSARs) are serious ADEs that have not previously been documented in the protocol or other safety information. SAEs which are attributed by the Investigator to the patient's underlying medical condition and unrelated to the study device will not be reported as SUSARs. The Sponsor is responsible for expedited reporting of SUSARs to the FDA; expedited reporting requires a preliminary report within 7 days for fatal or life-threatening cases, with another 8 days for completion of the report, and within 15 days for all other SUSARs.

The Investigator is responsible for notifying the Institutional Review Board (IRB).

12 STATISTICAL ANALYSIS

A Statistical Analysis Plan (SAP) will be prepared after the protocol and eCRF are approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it in the case of any differences.

The statistical evaluation will be performed using the Statistical Analysis Software (SAS®) Version 9.2 or higher (SAS Institute, Cary, NC). All data will be summarized using descriptive statistics, and where necessary, data will also be listed. For continuous variables, data will be summarized with the number of patients (N), mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, data will be tabulated with the number and proportion of patients for each category.

12.1 Determination of Sample Size

A sample size of 52 patients will have 80% power to detect a change from baseline to Week 5 of at least 0.35 points in the Wound-QoL global score (e.g., a baseline mean Wound-QoL global score of 3.53 and a follow-up mean Wound-QoL global score of 3.18), assuming an estimated SD of differences of 0.88, using a paired t-test with a 0.050 two-sided significance level. Patients who withdraw or are withdrawn before completion of the Week 2 assessments and the Week 3 Wound-QoL questionnaire will be replaced to ensure that at least 52 patients will complete the study.

12.2 Analysis Population

All patients who receive at least 2 weeks of study treatment and complete the Week 3 Wound-QoL questionnaire will be included in the primary analysis population used for all analyses. Additional populations may be explored and will be detailed in the SAP.

12.3 Disposition

Patient disposition will be summarized in terms of the number of patients who enter the study, the number who discontinue early, the number who complete the study and the number who are included in each relevant subgroup or baseline category.

12.4 Demographic and Baseline Characteristics

Demographic variables to be recorded include age, race, ethnicity, gender, body height, and body weight. Wound history to be recorded includes wound type(s), wound age(s), location(s), past complications, and current dressing change frequency. Also, screening length and width of the wound(s) will be recorded.

Demographic and baseline information will be summarized in tables using descriptive statistics.

12.5 Clinical Outcome Analyses

The global score of the Wound-QoL questionnaire will be summarized and explored in several ways. The primary analysis will be a paired t-test analysis of the mean global score of the Wound-QoL questionnaire at baseline and after 4 weeks of treatment. The global score of the Wound-QoL questionnaire may also be categorized to describe the proportion of patients with particular scores on individual questions, such as those with no score of 3 or 4 given, or to split the possible results into categories.

Secondary analyses include the changes from baseline in the subscores of the Wound-QoL questionnaire for the Body, Psyche, and Everyday Life QoL dimensions.

Exploratory analysis includes the change from baseline in the appearance and size of the wound(s).

All endpoints will be summarized using descriptive statistics.

Subgroup analyses may be performed based on such things as the size of the wound(s), the duration of treatment application, and the type of wound(s).

12.6 Safety Analysis

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities. The incidence of TEAEs (events with onset dates on or after the start of the study treatment) will be included in incidence tables. Events with missing onset dates will be included as treatment-emergent. If a patient experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study device will be used in the summary tables. SAEs, AEs causing discontinuation, and ADEs will be tabulated. All AEs will be listed by patient, along with information regarding onset,

duration, severity, relationship to study device, action taken with study device, treatment of event, and outcome.

Clinical laboratory data, vital signs, physical examination results, wound history, and medical history will be listed by patient.

Listings and summary tables will be provided for prior medications and for concomitant medications initiated or continued during the study period. Study treatment exposure will be listed by patient and summarized descriptively.

13 STUDY MANAGEMENT

13.1 Study-Specific Materials

In addition to the Study Products, the Sponsor will also supply the following items for this study:

1. Single-use, disposable rulers for wound measurements
2. Pens for marking bottles of Prontosan solution and Prontosan gel
3. Digital camera (with memory card) for wound size and appearance documentation

In addition, the study site will supply the patients with appropriate wound care materials (e.g., gauze, bandages, tape) for the care of their wound(s) while they are at home.

13.2 Approval and Consent

13.2.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the Code of Federal Regulations (CFR), and in compliance with good clinical practice (GCP) guidelines.

13.2.2 Institutional Review Board

Conduct of the study must be approved by an appropriately constituted IRB. Approval is required for the study protocol, any protocol amendments, and ICFs.

13.2.3 Informed Consent

For each study patient, written informed consent will be obtained prior to performing any protocol-related activities. As part of this procedure, the Investigator or designee must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study treatment in such a manner that the patient is aware of the potential risks, inconveniences, or adverse effects that may occur. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by the FDA and International Council for Harmonization guidelines. The Investigator will provide the Sponsor or its representative with a copy of the IRB-approved ICF prior to the start of the study.

13.3 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained.

Clinical data will be entered on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry (such as diaries). All study forms and records transmitted to the Sponsor must carry only coded identifiers such that personally identifying information is not transmitted. The primary method of data transmittal is via the secure, internet-based EDC system maintained by inVentiv Health Clinical. Access to the EDC system is available to authorized users via the study's Internet web site, where an assigned username and password are required for access.

Any changes made to data after collection will be made through the use of data clarification forms. eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

13.4 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

13.5 Record Retention

Study records and source documents will be maintained per local laws and regulations.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

13.6 Monitoring

The study will be monitored to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

On-site monitoring visits may be made on a "for cause" basis for quality purposes. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each patient.

The Investigator will make available to the clinical monitor source documents and medical records necessary to complete eCRFs. In addition, the Investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

13.7 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor may arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

13.8 Protocol Amendment and Protocol Deviation

13.8.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of patients or the conduct of the study will be classed as administrative amendments and will be submitted to the IRBs for information only. The Sponsor or its designee will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the IRBs for approval.

13.8.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor or its designee must be informed as soon as possible. Protocol deviations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB and in accordance with applicable FDA mandates is an Investigator responsibility.

13.9 Ethical Considerations

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR, and in compliance with GCP guidelines.

IRBs will review and approve this protocol and the ICF. All patients are required to give written informed consent prior to participation in the study.

13.10 Financing and Insurance

Prior to the study commencing, the Sponsor or its designee and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor or its designee.

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

13.11 Publication Policy

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or its designee. With respect to such rights, the Sponsor will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, Investigators will be required to assign all such inventions either to their Institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

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15 APPENDICES

Appendix 1: Wound-QoL Questionnaire

The Wound-QoL questionnaire (shown below) measures the health-related QoL of patients with chronic wounds.[14,15]

The following questions are designed to find out how your chronic wound(s) affect(s) your quality of life.

Please check one box per line!

	In the last seven days ...	not at all	a little	moderately	quite a lot	very much
1	...my wound hurt	O	O	O	O	O
2	...my wound had a bad smell	O	O	O	O	O
3	...the discharge from the wound has upset me	O	O	O	O	O
4	...the wound has affected my sleep	O	O	O	O	O
5	...the treatment of the wound has been a burden to me	O	O	O	O	O
6	...the wound has made me unhappy	O	O	O	O	O
7	...I have felt frustrated because the wound is taking so long to heal	O	O	O	O	O
8	...I have worried about my wound	O	O	O	O	O
9	...I have been afraid of the wound getting worse or of getting new wounds	O	O	O	O	O
10	...I have been afraid of hitting the wound against something	O	O	O	O	O
11	...I have had trouble moving around because of the wound	O	O	O	O	O
12	...climbing stairs has been difficult because of the wound	O	O	O	O	O
13	...I have had trouble with everyday activities because of the wound	O	O	O	O	O
14	...the wound has limited my recreational activities	O	O	O	O	O
15	...the wound has forced me to limit my contact with other people	O	O	O	O	O
16	...I have felt dependent on help from others because of the wound	O	O	O	O	O
17	...the wound has been a financial burden to me	O	O	O	O	O

Appendix 2: Wound Measurement with the Clock Method

Wounds are to be measured using the clock method with the standard, single-use, disposable rulers. With this technique, you will draw an imaginary box around the wound at the longest length and the greatest width of the wound, using the body orientation as an imaginary clock (12:00 is at the head, 6:00 is at the feet). Do not slant the ruler to accommodate the greatest measurement, and remember that sometimes length is smaller than width. You will measure the length and width, in centimeters (cm), of the imaginary box. To measure a wound on the feet, use the heels as 12:00 and toes as 6:00.[17]

To measure the greatest length of the wound (regardless of shape), use the following steps:

1. Picture the face of the clock lying over the wound bed with 12:00 pointing toward the patient's head and 6:00 toward the patient's feet.
2. Locate the part of the wound that is closest to 12:00 and draw a line (in your mind) from that point straight across the body.
3. Locate the part of the wound that is closest to 6:00 and draw another line (in your mind) from that point straight across the body.
    - Now you have 2 parallel lines framing the top and bottom of the wound.
4. Place a standard, single-use, disposable ruler between these 2 parallel lines to measure the greatest length in cm.

To measure the greatest width of the wound, use the following steps:

5. Locate the part of the wound that is closest to 9:00 and draw a line (in your mind) at that point straight up and down (head to foot).
6. Locate the part of the wound that is closest to 3:00 and draw another line (in your mind) at that point straight up and down.
    - Now you have 2 parallel lines framing the left and right sides of the wound, thus completing the imaginary box around the wound.
7. Place a standard, single-use, disposable ruler between these 2 parallel lines to measure the greatest width in cm.
8. Remember to document all measurements in cm.

At this point, you have the maximum length (instructions 1 to 4) and the maximum width (instructions 5 to 7) of the wound. You can now calculate the surface area of the wound (length x width) in cm^2. To qualify for this study, the wound must be between 5 cm^2 and 50 cm^2, inclusive.