A Pilot Randomized Controlled Trial to Evaluate an Advanced Borderless Dressing (ALLEVYN™ LIFE Non-Bordered) in the Treatment of Chronic Ulcers

Study Number:	CT1603ALF
Sponsor Name & Address:	Smith & Nephew, Inc. 5600 Clearfork Main Street Fort Worth, Texas 76109
Test and Comparator Product(s):	Test Article: ALLEVYN LIFE Non-Bordered Comparator Article: Standard Care
Protocol Author(s):	Stewart Richmond, PhD Michael Robinson, MMathStat Darrell Lange, PhD
Protocol Version	1.0, 27Mar2017

1. SIGNATURES

1.1 INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "A Pilot Randomized Controlled Trial to Evaluate an Advanced Borderless Dressing (ALLEVYN™ LIFE Non-Bordered) in the Treatment of Chronic Ulcers," version 1.0, dated 27 Mar 2017, and agree to abide by all provisions set forth therein.

I agree to comply with the requirements stipulated in Section 21.3 (Principal Investigator Obligations) of the protocol.

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

_____
Signature

_____ _____
Name of Principal Investigator (print) Date

1.2 SPONSOR APPROVAL

Andy Weymann, MD, MBA Senior Vice President and Chief Medical Officer, Clinical, Medical, and Scientific Affairs	Date	Jaime Dickerson, PhD Vice President, Global Clinical Operations	28 MAR 2017 Date
Alan Rossington, MEng, MSc Director Biostatistics and Data Management, Global Strategy	Date	D. Innes Cargill, PhD Director, Global Clinical Operations and Medical Monitor	3/28/17 Date
Beate Hanson, MD, PhD Vice President, Global Clinical Strategy	Date		

1.2 SPONSOR APPROVAL

Andy Weymann, MD, MBA Senior Vice President and Chief Medical Officer, Clinical, Medical, and Scientific Affairs	Date	Jaime Dickerson, PhD Vice President, Global Clinical Operations	Date
Alan Rossington, MEng, MSc Director Biostatistics and Data Management, Global Strategy	29/Mar/17 Date	D. Innes Cargill, PhD Director, Global Clinical Operations and Medical Monitor	Date
Beate Hanson, MD, PhD Vice President, Global Clinical Strategy	Date		

1.2 SPONSOR APPROVAL

Andy Weymann, MD, MBA Senior Vice President and Chief Medical Officer, Clinical, Medical, and Scientific Affairs	April 12, 17 Date	Jaime Dickerson, PhD Vice President, Global Clinical Operations	Date
Alan Rossington, MEng, MSc Director Biostatistics and Data Management, Global Strategy	Date	D. Innes Cargill, PhD Director, Global Clinical Operations and Medical Monitor	Date
Beate Hanson, MD, PhD Vice President, Global Clinical Strategy	April 12, 17 Date		

1.3 QUALITY ASSURANCE SIGNATURE

12APR17

Paul Martin
Senior Manager, Quality Assurance

Date

2. SYNOPSIS

Financial Disclosure Information for U.S. FDA Submission to be Obtained?	Yes	No
		X

Investigational Products:	ALLEVYN LIFE Non-Bordered
Product Used in Study:	ALLEVYN LIFE Non-Bordered is a borderless, multilayer foam dressing with a silicone adhesive.
Active Ingredients:	NA

Objective(s):

The primary objective is to estimate the effect of treatment with Allevyn Life Non-Bordered (ALNB) on Health-Related Quality of Life (HRQoL) in subjects with chronic ulcers, measured using the Cardiff Wound Impact Schedule Physical Symptoms and Daily Living (CWIS-PSDL) scale, compared to subjects receiving SC alone, over a six week treatment period.

Secondary objectives of this study are:

1) To estimate the effects of treatment with ALNB, when compared with SC alone, on:
    a. HRQoL measured by the CWIS-PSDL scale at three and twelve weeks, and CWIS well-being (WB), social life (SL); global quality of life (GQ); and satisfaction with quality of

life (SQ) scales; at three, six, and twelve weeks

b. Ulcer progression (including undermining, necrotic tissue type and amount, exudate type and amount, skin color surrounding the wound, granulation tissue, epithelialization, condition of peri-wound, ulcer dimensions and healing status) at three, six, and twelve weeks

2) Health care resource use related to the reference ulcer (including number and cost of dressings used, time in hospital, number and cost of additional treatments, procedures, and investigations) over twelve weeks

The exploratory objectives of this study are to compare differences between ALNB and SC in dressing performance (including wear time, leakage, odor control, and absorption under compression) and usability (including comfort and ease of application/removal together with associated pain) at three, six, and twelve weeks.

Study Population: Adults aged 18 years and older with moderate to highly exuding chronic ulcers.

Structure:	Parallel Group
Duration of Treatment:	Up to 12 weeks
Duration of Assessment:	Up to 12 weeks

Multi-Center:	[X] Yes Number of Centers: Up to 6 [ ] No

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

Randomization:	[X] Yes Group Assignment Ratio: 5:3 in favor of ALNB (ALNB n = 25; SC n = 15) Stratified by wound type: diabetic foot ulcer (DFU), leg ulcer (LU) and pressure ulcer (PU). [ ] No

Concurrent Comparator:	Standard Care (SC)

Estimated Total Sample Size:	A minimum of 40 randomized subjects.
Statistical Rationale Provided:	[ ] Yes [X] No
Subject Population:	Adult subjects (≥ 18 years of age) presenting with a moderate

to highly exuding chronic ulcer that, in the opinion of the Investigator, would benefit from a protective dressing but does not require topical antimicrobial treatment. Chronic ulcers will include leg ulcers (LU) of any etiology, pressure ulcers (PU), and nonischemic diabetic foot ulcers (DFU).

Variable(s):

PRIMARY: The change in CWIS-PSDL scale score between baseline and six weeks in each treatment group.

KEY SECONDARY: Subject-reported HRQoL variables (measured using the CWIS) to be compared between groups for change over three, six, and twelve weeks for the domains of CWIS-SL, CWIS-WB, and CWIS-GQ and at 3 and 12 weeks for CWIS-PSDL.

SECONDARY Ulcer progression variables to be compared between groups at three, six, and twelve weeks including:

- Modified Bates-Jensen Wound Assessment Tool
  - Undermining
  - Necrotic tissue type
  - Necrotic tissue amount
  - Exudate type
  - Exudate amount
  - Skin color surrounding the wound
  - Granulation tissue
  - Epithelialization
- Condition of peri-wound
- Ulcer dimensions
- Ulcer healed status

Healthcare resource use variables (to be compared between groups over the entire twelve week study period) including:

- Dressings used (number and type for both primary and secondary dressings), including use of compression therapy
- Healthcare consultations (number and type)
- Time spent by health care providers (HCP) in treating/caring for reference ulcer
- Time in hospital (nights spent as an inpatient due to reference ulcer)
- Interventions/procedures related to the reference ulcer (number and type), including debridement of the ulcer (curette, scissors, scalpel, forceps, other)
- Concomitant therapies/treatments (number and type) used on the reference ulcer

EXPLORATORY: Further exploratory data will be gathered for dressing performance and usability/acceptability and compared between groups, where appropriate. Relevant variables will include:

- Dressing wear time (days)
- Dressing leakage (HCP-assessed)
- Ease of dressing application/removal (HCP-assessed)
- Dressing use (whether dressing was cut and adherence following repositioning)
- Odor control of dressing (HCP-assessed)
- Absorption under compression (HCP-assessed for subjects with LU requiring compression).
- Reason for dressing change (HCP-assessed)
- Pain on dressing removal (subject-reported)
- Comfort during wear (subject-reported)

SAFETY: Safety data will be gathered throughout the twelve weeks of the study, including:

- Adverse events
- Device deficiencies

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3.4 LIST OF ABBREVIATIONS

Abbreviation	Definition
ABI	Ankle Brachial Index
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
ALNB	ALLEVYN LIFE Non-Bordered
ASADE	Anticipated Serious Adverse Device Effect(s)
cm	centimeter
CWIS	Cardiff Wound Impact Schedule
DevD	Device Deficiency(ies)
DFU	Diabetic Foot Ulcer
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GQ	Global Quality of Life
HCP	Health Care Provider
HRQoL	Health-Related Quality of Life
IAD	Incontinence-Associated Dermatitis
IRB	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
ISF	Investigator Site File
ITD	Intertriginous Dermatitis
LTFU	Lost To Follow-Up
LU	Leg Ulcer
MARSI	Medical Adhesive-Related Skin Injury
MASD	Moisture-Associated Skin Damage

Abbreviation	Definition
MedDRA	Dictionary for Medical Drug Regulatory Activities
MVP	Moisture Vapor Permeable
NPUAP	National Pressure Ulcer Advisory Panel
PMS	Post-Marketing Surveillance
PP	Per-Protocol set
PSDL	Physical Symptoms of Daily Living
PU	Pressure Ulcer
QoL	Quality of Life
RCT	Randomized Clinical Trial
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System Software, Cary, NC, USA
SC	Standard Care
SL	Social Life
S&N	Smith & Nephew Inc.
SOP	Standard Operating Procedure
SQ	Satisfaction with Quality of Life
UADE	Unanticipated Adverse Device Effect(s)
USADE	Unanticipated Serious Adverse Device Effect(s)
VLU	Venous Leg Ulcer
WB	Well Being

4. INTRODUCTION

4.1 BACKGROUND

Chronic wounds, including leg ulcers (LU), diabetic foot ulcers (DFU), and pressure ulcers (PU), significantly impact patients' quality of life. These chronic wounds fail to heal and remain stuck in an inflammatory phase. In developed countries, the incidence of chronic wounds has increased in recent years[1], possibly due to an aging population with an abundance of concurrent illnesses such as diabetes, hypertension, obesity, and peripheral vascular disease.

In the United Kingdom, it is estimated that 15 to 18 out of 1000 people suffer from VLU; the cost to treat these and other chronic wounds was between £2-3 billion in 2006[2]. More recent estimates put the annual cost of treating chronic wounds in the US at $6-15 billion[3], however, a 2010 report[4] puts the cost of treating DFU alone at $39 billion.

Closure of complex wounds, including chronic wounds, post-surgical wounds, and trauma wounds is often achieved through secondary intention. Although these wound types have different etiologies and underlying pathophysiology, their treatment follows a similar course. Wound closure by secondary intention can be supported by a wide range of wound dressings designed specifically for this purpose. An ideal dressing must provide the following at a minimum:

- a barrier to exogenous contamination and infection
- adequate management of wound exudate
- maintenance of a moist wound healing environment

Failure of a dressing to deliver these fundamental features will negatively impact the ability of a complex wound to heal and may allow the wound to deteriorate. Failure to prevent contamination may allow a wound to become infected. Inability to manage moderate to high exudate volume may lead to maceration of the peri-wound skin, which can lead to further wound breakdown if untreated. At the same time, a dressing should not allow a wound to dry out; the dressing should maintain a moist wound healing environment. The consequences of wound

deterioration vary, but can result in protracted wound healing or may cause an otherwise preventable hospital episode for surgical management or closure.

This study will focus on the use of ALLEVYN LIFE™ Non-Bordered (ALNB) in the treatment of chronic wounds. ALNB is a new multilayer foam dressing that is intended to provide an optimal moist wound healing environment to promote the healing of moderate and highly exuding wounds.

ALNB is the latest addition to the ALLEVYN LIFE range of dressings, which were first launched in 2012. The introduction of ALNB recognizes the fact that clinicians sometimes prefer using a non-bordered absorbent product with wounds that require a secondary dressing, e.g. compression bandaging for leg ulcers.

While the present study will be the first clinical trial to evaluate the actual use of ALNB in clinical practice, the original ALLEVYN LIFE dressing has been used in several clinical studies. The results of these suggest that ALLEVYN LIFE supports good wound progression, wound granulation, healthy condition of the surrounding skin, and patient satisfaction[5].

Because medical devices are designed to improve the patient's quality of life[6], the primary outcome in the study will be the differences in Health-Related Quality of Life (HRQoL) between subjects treated with ALNB and Standard Care (SC) for subjects with moderate to highly exuding chronic wounds. The subjects will be surveyed using the Cardiff Wound Impact Schedule (CWIS)[7] which measures the impact of chronic wounds on physical symptoms, daily living, social life, and well-being.

A summary of known and potential risks and benefits to humans of the test article can be found in the Package Insert (ALLEVYN LIFE Non-Bordered).

4.2 SAFETY CONSIDERATIONS

Precautions for the use of ALNB, as specified in the current Instructions for Use (IFU), are:

- Do not use with oxidizing agents such as hypochlorite solutions (e.g. EUSOL) or hydrogen peroxide, as these can reduce the absorbency of the dressing.

- If reddening or sensitization occurs discontinue use.
- Single-use only; if used on more than one subject, cross contamination or infection may occur.
- Once the pouch is opened, do not retain unused dressings for application at a later date.

Risks associated with the use of ALNB within the present study will be mitigated as follows:

- Study personnel will be trained in the correct use of ALNB prior to applying the dressing to the wounds of study subjects.
- Study personnel will be trained on the study protocol.
- Study personnel will be directed to carefully follow the inclusion and exclusion criteria for participation in the study when assessing the subject eligibility.
- Study personnel will be directed to read and follow the IFU.

4.2.1 Benefits

ALNB is a multilayer dressing with a silicone gel adhesive that provides an optimal moist wound healing environment to promote the healing of moderate and highly exuding wounds.

The absorbent pad is composed of a foam layer and a lock-away core made from superabsorbent material. The silicone adhesive layer is gentle, even to fragile skin, and makes it easy to apply, reposition, and remove. A breathable opaque outer film helps mask exudate, prevent bacterial contamination, and is showerproof when used with appropriate secondary retention.

4.2.2 Hazards/Harms

This will be the first study to evaluate the use of ALNB in clinical practice; there is currently no direct clinical evidence concerning the safety of ALNB.

ALLEVYN LIFE has been used widely over the last four years and has been shown to be equivalent to ALNB with regard to materials and fluid handling properties (see Section 6). Published clinical studies with ALLEVYN LIFE, risk management reports, and post-marketing

surveillance (PMS) data consistently indicate that the risk of adverse events is low and that reactions which do occur are generally local to the application site and are mild in severity. Adverse events are well characterized and are manageable in the majority of cases. As such, ALLEVYN LIFE demonstrates an acceptable benefit-risk profile.

Because of the similarities between ALLEVYN LIFE and ALNB, the anticipated medical benefits of ALNB are also expected to outweigh risks. There are some differences between the two products, including:

- ALNB can be cut to size without compromising its performance characteristics
- ALNB does not incorporate a change indicator, as this would be obscured by any secondary dressing
- ALNB includes a lower tack adhesive, to serve as a 'third hand', and enable the dressing to be removed and repositioned more easily
- ALNB requires the use of a secondary dressing to aid retention

The use of a lower tack adhesive with ALNB may positively impact safety by lowering the incidence and severity of skin stripping resulting from its use. Unlike ALLEVYN LIFE, ALNB requires a secondary dressing to aid retention. Choice of ancillary dressing, together with associated risks relating to this secondary device, will be carefully monitored during this study.

There are no anticipated Serious Adverse Device Effects (SADE) associated with the use of ALNB.

5. OBJECTIVES

The aim of this pilot randomized controlled trial (RCT) is to gather preliminary clinical, health economic and safety data on the use of ALNB in the treatment of chronic wounds, for post-market surveillance and to assist with planning future research concerned with the efficacy and cost-effectiveness of ALNB.

5.1 PRIMARY

The primary objective is to estimate the effect of treatment with ALNB on HRQoL in subjects with chronic ulcers, measured using the CWIS-PSDL (Physical Symptoms of Daily Living) scale, compared to subjects receiving SC alone, over a six-week treatment period.

5.2 KEY SECONDARY

To estimate the effects of treatment with ALNB, when compared with SC alone, on HRQoL measured by the CWIS-PSDL scale at three and twelve weeks, and CWIS well-being (WB), social life (SL); global quality of life (GQ); and satisfaction with quality of life scales (SQ); at three, six, and twelve weeks.

5.3 SECONDARY

Secondary objectives of this study are:

- Ulcer progression (including undermining, necrotic tissue type and amount, exudate type and amount, skin color surrounding the wound, granulation tissue, epithelialization, condition of peri-wound, ulcer dimensions and healing status) at three, six, and twelve weeks
- Healthcare resource use related to the reference ulcer (including number and cost of dressings used, consultations and time used by healthcare professionals (HCP), time in hospital, number and cost of additional treatments, procedures, and investigations) over twelve weeks

5.4 EXPLORATORY

The exploratory objective of this study is to compare differences between ALNB and SC in dressing performance (including wear time, leakage, odor control, and absorption under compression) and usability (including comfort and ease of application/removal together with associated pain) at three, six, and twelve weeks

5.5 SAFETY

Safety data will be gathered throughout the twelve weeks of the study including:

- Adverse events
- Device deficiencies

5.6 CLAIMS

The study is a pilot RCT, which will enroll a small sample of subjects with a range of chronic, moderate to highly exuding ulcer types: LU (arterial/mixed etiology leg ulcers or venous leg ulcers requiring compression therapy), PU, and non-ischemic DFU. Data generated from this study are unlikely to be sufficient to demonstrate any statistically significant difference in observed clinical outcomes between devices. Nevertheless, this study will generate the first comparative clinical, economic, and safety data for use of ALNB in subjects, and will extend current evidence for the ALLEVYN LIFE product range.

This pilot RCT may provide preliminary data as supporting evidence for the existing product claims.

6. STUDY PRODUCT

6.1 IDENTIFICATION

6.1.1 Test Product: ALLEVYN LIFE Non-Bordered

Intended use

ALNB is intended for use in wound management by secondary intention on shallow, granulating wounds, chronic and acute exudative wounds, full- and partial-thickness wounds including:

- Pressure ulcers
- Leg ulcers
- Diabetic foot ulcers
- Surgical wounds
- First- and second-degree burns

- Skin graft donor sites
- Skin tears
- Fungating wounds

The present study aims to evaluate the use of ALNB for adult (≥ 18 years of age) subjects with moderate to highly exuding chronic ulcers that, in the opinion of the Investigator, would benefit from a protective dressing but do not require a topical antimicrobial treatment, limited to:

- Pressure ulcers, excluding Stage 1. Inclusion of other stages, including "unstageable", depends on the level of exudate and lack of infection.
- Non-ischemic diabetic foot ulcers (Wagner Grade 1 or 2)
- Leg ulcers

Dressing description

ALNB is a quadrilobed or rectangular shaped exudate management wound dressing which is a new variant of ALLEVYN LIFE. ALNB is a non-bordered dressing, allowing it to be cut to the shape of the wound before use. ALNB uses a low-tack silicone adhesive. ALNB incorporates an opaque, moisture-vapor permeable (MVP) top film that allows for some masking of the exudate penetration.

Construction of ALNB

ALNB is a composite dressing; it is made up of 4 layers (see Figure 6.1.1-1), including the MVP top film, a superabsorbent layer, a foam layer, and a wound contact layer (see Figure 6.1.1-2). The wound contact layer is perforated to allow the transfer of exudate from the wound into the dressing.

Figure 6.1.1-1: ALLEVYN Life Non-Bordered Dressing Structure

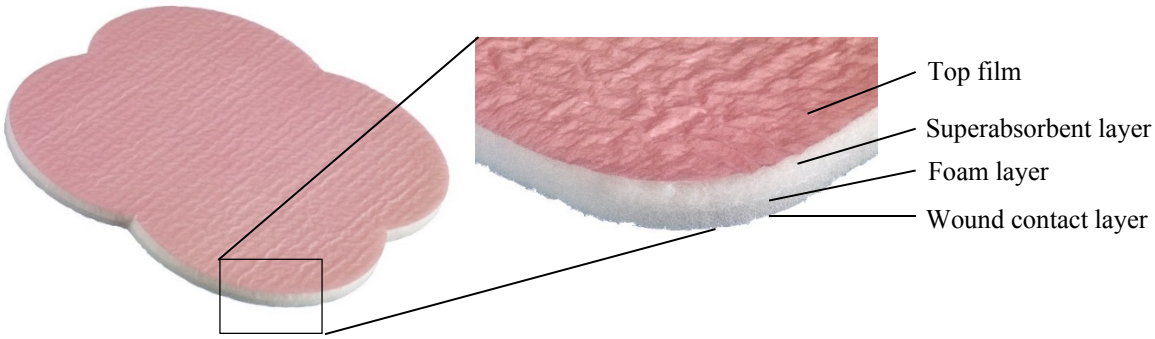
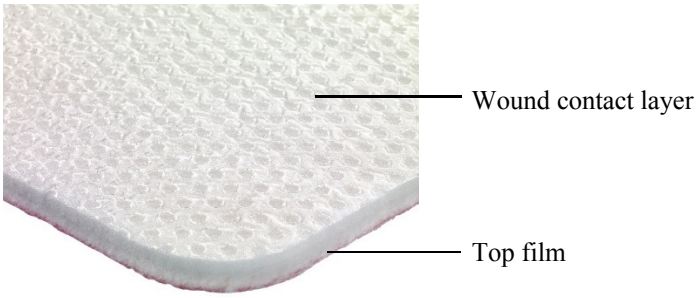


Figure 6.1.1-2: Wound Contact Layer, Showing Regular Perforation



The device is fitted with handles to protect the silicone wound contact layer prior to application and to facilitate application of the dressing to the wound. The handles are removed during the application process.

Manufacturer and available sizes

ALNB is manufactured by Smith & Nephew Medical Limited, 101 Hessle Road, Hull, HU3 2BN, England.

ALNB is available in three sizes (see Table 6.1.1-1). Shapes and relative sizes are shown in Figure 6.1.1-3.

Table 6.1.1-1: ALLEVYN Life Non-Bordered Dressings for Evaluation

Product Code	Dressing Size and Packaging
66801748	10.5 x 10.5 cm Dressing; Carton of 10
66801749	16 x 16 cm Dressing; Carton of 10
66801751	10 x 20 cm Dressing; Carton of 10

Figure 6.1.1-3: ALLEVYN LIFE Non-Bordered Dressings (Not Actual Size)

Number of investigational devices used on each subject

ALNB is designed to be worn for up to seven days. Subjects randomized to ALNB will have their dressings changed according to individual clinical need (see Section 6.2). The total duration of treatment with ALNB will also depend on factors such as wound healing, topical wound treatments, or suitability of continued treatment with ALNB. If the wound does not heal, the maximum study treatment period will be twelve weeks. Thus, the number of ALNB dressings used by each subject will differ.

6.1.2 Comparator Products

Subjects allocated to the comparator arm of the study shall receive SC, defined as any protective wound dressing(s) which, in the opinion of the Investigator, would be beneficial in treating the wound, other than:

- variants of ALLEVYN
- topical antimicrobials, such as Acticoat™, Iododsorb™, silver products, etc.
- negative pressure wound therapy

Standard care should correspond as closely as possible to normal clinical practice, and dressings used routinely within each individual research site.

6.1.3 Ancillary Product

At Smith & Nephew's discretion, the following ancillary products may be made available to research sites for use on study subjects during this study – OPSITE™, PROFORE™, DURAFIBER™, and INTRASITE™. However, this study does not require any particular ancillary dressing to be used to secure ALNB. Rather, selection of ancillary dressings should be determined based on clinical requirements.

Per the IFU, physicians may use INTRASITE under ALNB, as clinically warranted.

6.2 PRODUCT USE

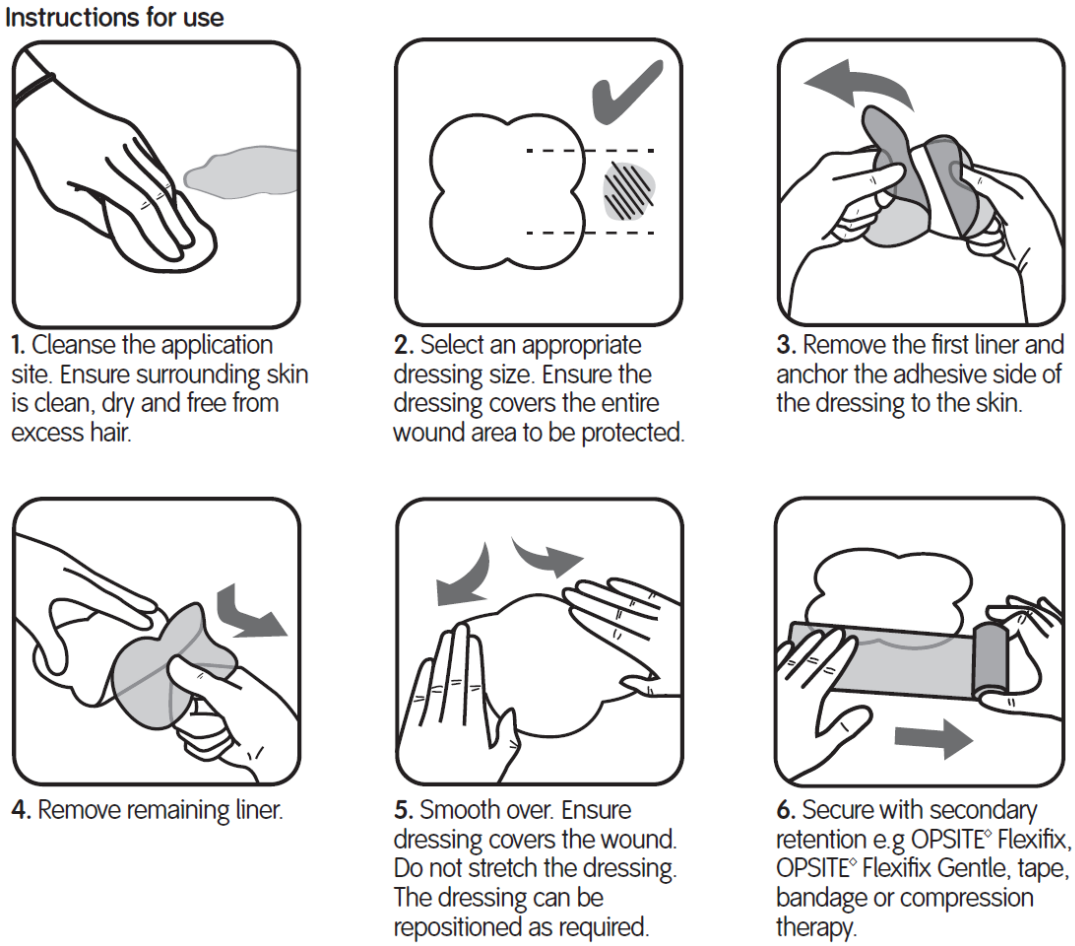
6.2.1 HCP Training

Study center personnel with responsibilities for the medical care of subjects and/or application of the investigational product (ALNB) will be trained on the use and application of ALNB prior to enrolling subjects into the study. HCP training will only occur following completion of the clinical trial agreement. HCP training will involve a presentation on the correct application and use of ALNB, including frequency of dressing change. ALNB is a moderate to highly absorbent dressing which can be worn for up to seven days and should be changed as directed in the product IFU (see Sections 6.2.3 and 21.1), rather than due to routine schedule or convenience.

6.2.2 Application

Application of the product will follow the directions from the product IFU (Figure 6.2.2-1).

Figure 6.2.2-1: ALNB Application

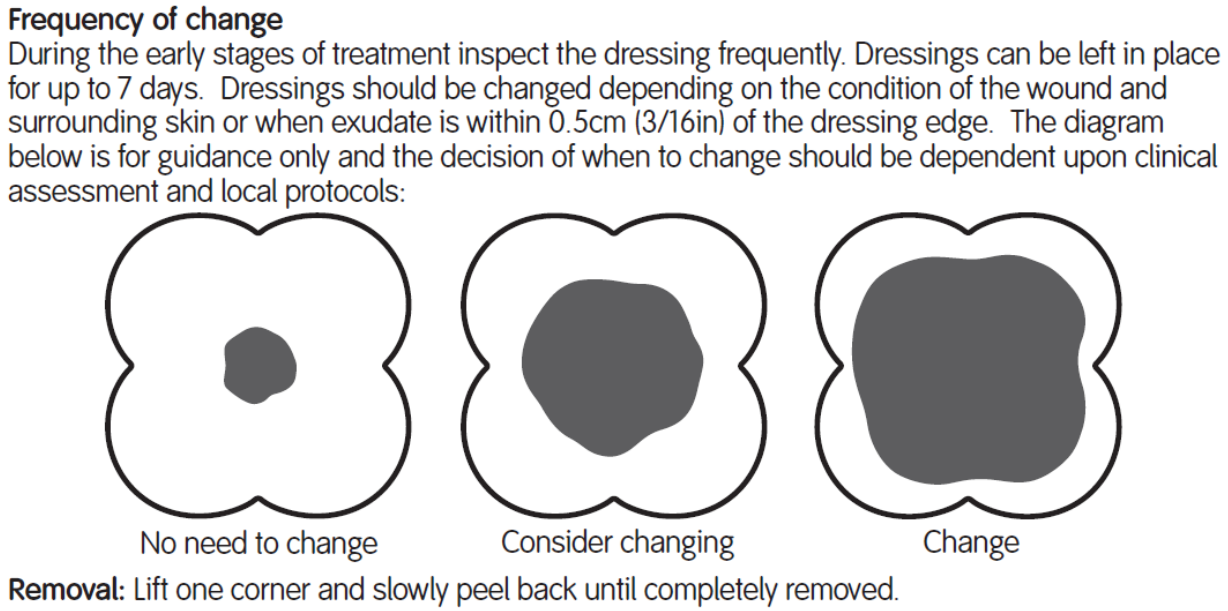


Study subjects will not be trained or expected to apply or change their own dressings. All dressing changes should occur at the Investigator site.

6.2.3 Dressing Change

HCP will be instructed to follow directions given in the product IFU (Figure 6.2.3-1) when changing ALNB.

Figure 6.2.3-1: Instructions for changing ALNB



6.2.4 Storage of ALNB

ALNB should be stored in a dry place, at less than 77°F (25°C), and away from sunlight.

6.2.5 Concomitant Dressings

With the exception of dressing/bandaging placed over ALNB for secondary retention or compression, the only other dressings that are permitted to come into contact with the wound bed and for use in conjunction with ALNB within the study are:

- Intrasite Gel for necrotic and sloughy wounds
- Durafiber for deeper wounds (Durafiber Ag should not be used due to its antimicrobial action).

6.3 PACKAGING AND LABELING

Packaging and labeling will be prepared to meet regulatory requirements.

6.3.1 Test Product

Smith & Nephew will supply each site with ALLEVYN LIFE Non-Bordered for use during the study. All test articles will be supplied in standard commercial packaging, clearly showing the batch number and expiry date. A label with the following information will be affixed to the ALNB packaging without obscuring any regulatory text:

- Smith & Nephew, Inc. Fort Worth, Texas
- Study Number
- Store at room temperature
- For Investigational Use Only

6.3.2 Comparator Article

SC, as defined in Section 6.1.2., will serve as the control treatment. Dressings used as SC will be those used routinely by the participating research site. Participating sites will acquire these routine dressings for use during the study.

Due to the variability in the product that will be used in the comparator group, S&N will not supply or label these dressings.

6.3.3 Ancillary Products

Any ancillary products supplied by Smith & Nephew will not be labeled.

6.4 PRODUCT ACCOUNTABILITY PROCEDURES

The Sponsor will keep a detailed record of all ALNB dressings supplied to each site. Confirmation of receipt by the Investigator will also be retained.

The receipt and dispensing of each dressing will be recorded on appropriate accountability forms available for verification by the Sponsor or its designated representative at each monitoring visit. Overall accountability for the accuracy of these records is the responsibility of the Investigator or designated individual maintaining the inventory, which shall include details of receipt, use,

waste, returns, and collection, etc., of product supplies. Used dressings will be appropriately destroyed per local requirements for clinical waste by the site staff without verification by the study monitor.

All cartons will be clearly identified per the labeling in Section 6.3. The Study Monitor will ensure that the procedures and records are in place for appropriate reconciliation of all test articles. As part of monitoring, the Study Monitor will check that the site personnel are following the procedures and completing all of the necessary documentation.

In addition, any ancillary products (PROFORE, INTRASITE, etc.) supplied to the site by the Sponsor will require appropriate accountability.

7. SUBJECTS

7.1 SUBJECT POPULATION

Approximately 40 adult subjects (18 years of age or older) with a moderate to highly exuding chronic ulcer that requires a dressing, but which does not, in the opinion of the Investigator, require topical antimicrobial treatment, will be recruited.

Chronic wounds will include LU (arterial/mixed etiology leg ulcers or venous leg ulcers requiring compression therapy), PU, and non-ischemic DFU. For subjects with multiple ulcers, the largest ulcer meeting the inclusion/exclusion criteria will be studied as the reference ulcer.

The following minimum numbers of wound types will be enrolled in each study group:

- ALNB: 5 DFU, 5 PU, 5 LU
- SC: 3 DFU, 3 PU, 3 LU.

7.2 INCLUSION CRITERIA

1. The subject must provide informed consent to participate in the study; see Section 9.1.
2. The subject must be eighteen (18) years of age or older.
3. The subject must be willing and able to make all required study visits.

4. The subject must be able to follow instructions and be deemed capable of completing the CWIS questionnaire.
5. The subject must present with a chronic (≥ 4 weeks duration) ulcer which meets all of the following criteria:
   (a) The ulcer is classified as either:
      - a pressure ulcer
      - a non-ischemic diabetic foot ulcer
      - a leg ulcer (arterial/mixed etiology leg ulcers or venous leg ulcers requiring compression therapy)
   (b) The ulcer is, in the opinion of the Investigator, moderate to highly exuding.
   (c) The ulcer would, in the opinion of the Investigator, benefit from a protective dressing.
   (d) The ulcer is not infected based on clinical signs/symptoms.
6. A subject with a DFU must have an ankle-brachial index (ABI) of 0.7 or greater, as measured within 30 days of the Screening Visit.

   Subjects with a VLU that will use compression therapy should have an ABI that meets the requirements of the IFU for the selected compression device.

7.3 EXCLUSION CRITERIA

1. Contraindications or hypersensitivity to the use of the ALLEVYN LIFE Non-Bordered, comparator, ancillary products, or their components.
2. Participation in the treatment period of another clinical trial within 30 days of Visit 1 or planned participation overlapping with this study.
3. The subject's reference ulcer is being treated with a topical antimicrobial dressing.

4. Subjects with skin features (e.g. tattoos, skin color, pre-existing scarring) which, in the opinion of the Investigator, could interfere with the study assessments.
5. Subjects who have participated previously in this clinical trial.
6. Subjects with a history of poor compliance with medical treatment.
7. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.

7.4 SCREENING LOG

Participating study sites are required to document all screened subjects initially considered for inclusion in this study (i.e. a subject who gives informed consent). If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and noted on the Screening Log.

7.5 ENROLLMENT

The point of enrollment in the study is when the subject has signed and dated the informed consent document and met all the eligibility criteria.

The anticipated enrollment period is approximately nine (9) months.

7.6 WITHDRAWAL

Subjects may be withdrawn early from study treatment for the following reasons:

- Closure of the reference ulcer.
- If the subject misses two (2) consecutive dressing changes/study visits, interrupting treatment for longer than seven (7) days.
- At the discretion of the Investigator due to:
    - A change in treatment that is clinically warranted
    - An adverse event (AE)

- Any other significant reason identified by the Investigator

Subjects may be withdrawn entirely from the study for the following reasons:

- At their own request (i.e. withdrawal of consent).
- Failure to complete the CWIS appropriately at Visit 1.
- At the discretion of the Investigator due to:
  - Concurrent illness
  - Adverse device effects (ADE)
  - Non-compliance (e.g. did not follow instructions).
  - Lost to follow-up (LTFU)
  - Any other significant reason identified by the Investigator

Where subjects withdraw consent, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's privacy.

Subjects withdrawn from the study because the CWIS is not complete will be replaced by enrolling a new study subject.

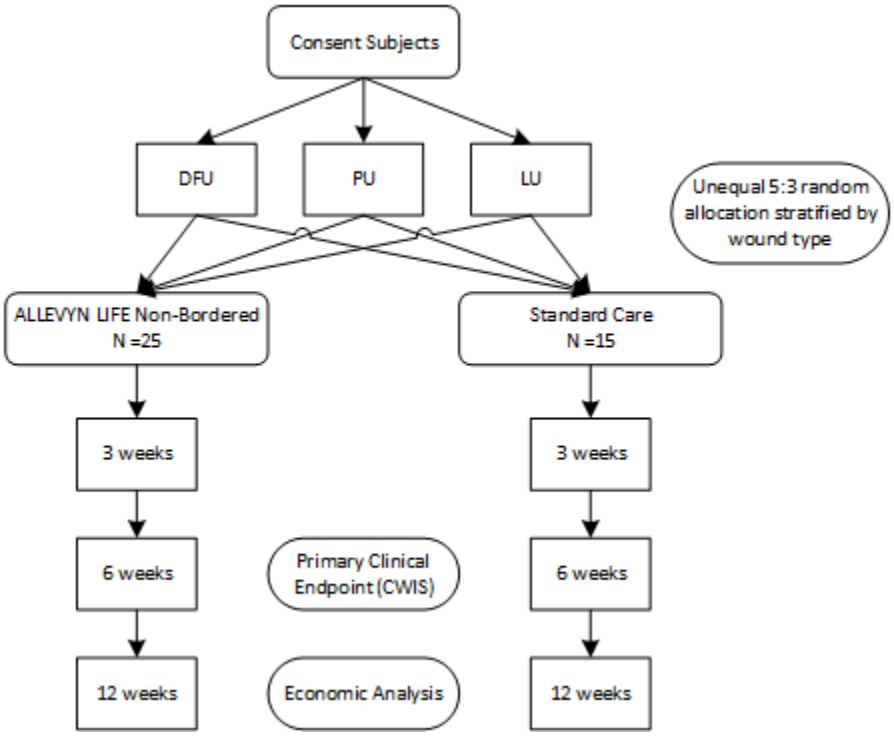
8. STUDY DESIGN

8.1 STUDY DESIGN

This is a randomized, parallel group study. Subjects will be randomly assigned in a 5:3 ratio of ALNB:SC. Subjects will be stratified by ulcer type (PU, DFU, LU).

Participation in the study will last up to 12 weeks. Subjects will be required to make at least one visit per week to the research site. The primary clinical endpoint will be six (6) weeks from enrollment, with clinical data also collected at three (3) and twelve (12) week follow-up visits. Health care resource use data will be gathered and compared over the entire twelve week study period.

Figure 8.1-1: Overview of Study Design



8.2 RATIONALE

This post-market clinical study is required for regulatory purposes and will be the first clinical evaluation of ALNB following its launch. This pilot study will gather preliminary data regarding the use of this new dressing in subjects with chronic, moderate to highly exuding ulcers in an outpatient clinical care setting. Both subject population and setting were selected due to market considerations. When compared to SC, this study will provide important evidence to support product claims, reinforce continuing regulatory approval, and provide both an estimate of effect size and test of study feasibility to guide the development of potential future full-scale RCT testing the efficacy and cost-effectiveness of ALNB.

The impact of treatment on HRQoL is a common outcome across a wide range of health interventions and medical conditions, including advanced wound care. The CWIS was chosen for use in this study due to its focus on the quality of life in subjects with chronic wounds, and supporting evidence for reliability and validity. Within this self-reported questionnaire, the

CWIS-PSDL scale was selected as the primary outcome measure due to relevance to key product claims for ALNB, including those concerning fluid handling/leakage, pain, comfort, and odor control.

In addition to evaluating the impact on quality of life, this study will also seek to estimate the effects of ALNB on ulcer progression, healthcare resource use, gather safety data, and explore dressing performance.

8.3 METHODS USED TO MINIMIZE BIAS

Blinding of subjects and HCP to treatment allocation is not possible due to obvious physical differences in the appearance of dressings and sterile packaging. Bias reduction will consist of subjects randomly allocated to the two groups, ALNB and SC, to control for the influence of extraneous variables on treatment outcomes. In this way, no Investigator will be able to direct a particular subject to a particular treatment. Baseline procedures and assessments are performed prior to assigning the subject to a treatment group. SC was selected as the comparator treatment, rather than a specific competitor dressing, together with the recruitment of subjects from multiple treatment facilities to widen the generalizability of results to normal clinical practice.

Unequal allocation of subjects in favor of ALNB will ensure that twenty-five (25) subjects receive treatment with ALNB, which is viewed as a reasonable minimum requirement in providing basic safety data for the primary dressing of interest. Additionally, treatment allocation will be stratified by ulcer type to safeguard against major imbalances in clinical characteristics at baseline and aid comparability between groups.

9. STUDY PROCEDURE

9.1 INFORMED CONSENT

Before conducting any study procedures or examinations, the purpose and nature of the study will be explained to the subject in their native language. The subject will then read, sign, and date the Institutional Review Board (IRB)-approved informed consent document (see below for difficulties with reading and writing). Additionally, the individual who obtains consent from the

subject will sign and date the informed consent document. A photocopy of the signed informed consent document will be provided to the subject and a copy will be placed in the subject's medical record, with the original filed in the Investigator site file (ISF). Any additional requirements required by the IRB will be followed.

Subjects lacking mental capacity

The minimum age for participation in the study is eighteen (18) years. Adults who lack the mental capacity to understand study information and provide informed consent without assistance from a legally appointed representative will not be permitted to take part in the study. This criterion is necessary due to demands of study participation, including completion of self-reported outcome measures.

Difficulties with reading or writing

If the subject is unable to read or write, the informed consent document and associated study information will be read aloud to the subject in the presence of an independent witness. If possible, the subject shall sign and personally date the informed consent form. Where this is not possible the subject will provide verbal consent to participate in the study. The witness will then personally sign and date the informed consent form, attesting that the information was accurately explained and that the informed consent was freely given.

9.2 VISITS AND EXAMINATIONS

9.2.1 Summary

For a summary of the required procedures by visit, see Table 9.2-1.

Table 9.2-1: Study Plan

Procedure	Key Visits				Other Visits	
	Visit 1 (Baseline)	**Visit 2** (Day 21±3) and **Visit 3** (Day 42±4)	**End of Study Visit** (Day 84±4)		**Routine Dressing Changes**	**Treatment D/C** (before end of study)
Informed Consent	√					
Demographics/Medical History	√					
Concomitant Medication	√	√	√		√	√
CWIS	√	√	√			√
Ulcer Assessment	√	√	√		√	√
ABI	√[1]					
Verify Inclusion/Exclusion	√					
Allocate Study ID Number	√					
Randomize	√					
Photograph Ulcer	√	√	√		√[2]	√
Photograph Dressing	√[3]	√	√		√[3]	√[3]
Dressing Change		√			√	
Complete Questions about Dressing (Subject and Investigator)	√	√	√		√	√
Pain scale		√	√		√	
Record Adverse Events (AE)	√	√	√		√	√
Record Device Deficiencies (DevD)	√	√	√		√	√
Complete Exit Form			√			

[1] If not obtained within last 30 days for DFU/LU subjects
[2] Only if AE related to ulcer is observed
[3] Only if DevD observed

9.2.2 Visit 1 – Initial Visit (Baseline, Day 1)

1. Obtain written informed consent from the subject as detailed in section 9.1.
2. Obtain demographic information, relevant medical history, and relevant concomitant medications.
3. Screen the subject against protocol inclusion and exclusion criteria.
4. Provide the subject with a copy of the CWIS, and allow sufficient time to complete it. Staff should not assist the subject with the questionnaire, other than to instruct the subject to complete all questions. Ensure that the subject has completed the CWIS questionnaire appropriately, providing a single valid response for each item of the questionnaire.

   NOTE: subjects who cannot read/write may have the CWIS read aloud to them and the subject's responses recorded. Ensure this process is noted in the source documents.
5. Complete an ulcer assessment (see Section 9.5.1) including ulcer classification, i.e. pressure ulcer staging or Wagner classification for DFU (see Section 9.5.5).
6. If the reference ulcer is a DFU or LU, determine ABI. Values obtained within the last 30 days may be used to qualify the subject.

   Note for DFU subjects: Subjects with a DFU and an ABI value less than 0.7 may not be enrolled.

   VLU subjects that will use compression during the study should have an ABI that meets the requirements stated in the IFU for the selected compression device.
7. Assign the subject a study number and allocate the subject to either the ALNB (experimental) or SC (comparator group) according to the randomization schedule provided by SealedEnvelope.

8. Photograph the ulcer. Ensure that the calibration ruler with subject's initials and visit date is visible in the image. If the ulcer is debrided, take a photograph of the ulcer immediately prior to and following debridement. Record any debridement and the method of debridement in the electronic Case Report Form (eCRF).
9. Apply dressing according to randomization:
    - For subjects allocated to the ALNB group, apply ALNB as instructed in Section 6.2.2.
    - For subjects allocated to SC, apply a suitable dressing per dressing IFU.
10. Record details of all dressings used for all subjects, (e.g. brand, size, etc.) as well as any treatment applied underneath the dressing, such as Durafiber or Intrasite gel.
11. Assess the ease of applying the dressing (Section 9.5.7), including remains in place and repositioning (if applicable).
12. Instruct the subject to carefully follow the ulcer care instructions until the next dressing change and provide information concerning arrangements for future study visits.
13. Record the total time that the subject spent at the visit (start to finish of ulcer care procedures).
14. If any AE or DevD are observed or reported after application of study product, they must be reported as instructed in Section 12 (Adverse Events and Device Deficiencies). In addition to photographing the ulcer (as above), photograph the dressing if reporting a device deficiency.

9.2.3 Routine Dressing Changes

As ALNB has a maximum recommended wear time of 7 days, routine dressing changes will occur between scheduled Study visits 2, 3, and the End of Study Visit. The number of these visits will vary from subject to subject, based on clinical judgment. These visits will involve subjects

returning to an on-site visit. Dressings should not be given to study subjects; the dressing should only be changed by an HCP at a visit.

1. Question subjects regarding any changes in health or concomitant treatment.
2. Ask the subject to assess the comfort of wearing the dressing since the last visit (see Section 9.5.8).
3. Assess the movement of the dressing (see Section 9.5.9).
4. Remove the old dressing and inspect the ulcer. Complete an ulcer assessment (see Section 9.5.1).
5. Assess the level of pain experienced by the subject when the dressing is removed (see Section 9.5.6).
6. Assess the ease of dressing removal, leakage, and absorption under compression (see section 9.5.10).
7. If any adverse events or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 (Adverse Events and Device Deficiencies).

   NOTE: Photograph the ulcer only if reporting an AE or DevD.
8. Redress the ulcer, if clinically indicated per the subject's randomization assignment:
   - For subjects allocated to the experimental group, apply ALNB as supplied for use in the study, cutting the dressing to size if required and securing with a suitable secondary dressing.
   - For subjects allocated to SC apply a suitable protective dressing, other than ALLEVYN LIFE/ALNB.
9. Record details of all dressings used for all subjects, (e.g. brand, size, etc.) as well as any treatment applied underneath the dressing, such as Durafiber or Intrasite gel.

   For subjects randomized to ALNB, record whether or not the dressing was cut to a smaller size.

10. Assess the ease of applying the dressing (see Section 9.5.7), including remains in place and repositioning (if applicable).
11. Instruct the subject to carefully follow the ulcer care instructions until the next dressing change and provide information concerning arrangements for future study visits.
12. Record the total time that the subject spent at the visit (start to finish of ulcer care procedures).
13. If any AE or DevD are observed or reported after application of study product, they must be reported as instructed in Section 12 (Adverse Events and Device Deficiencies).

9.2.4 Visit 2 (Day 21 ± 3 days) and Visit 3 (Day 42 ± 4 days)

Visits 2 and 3 will consist of an on-site visit. These visits should coincide with the normal timing of dressing changes, i.e. seven (7) days or fewer for ALNB.

Subjects who have already had their treatment discontinued/been withdrawn from treatment and no longer require a dressing change shall be followed up either by an on-site visit or by telephone. In such cases, the main purpose will be to collect CWIS outcome data and any data related to AE (if applicable).

1. Question subjects regarding any changes in health or concomitant treatment.
2. All subjects must complete the CWIS, including those withdrawn from treatment unless they have been withdrawn from the study.

   Give the subject a printed copy of the CWIS and allow sufficient time to complete it. Assist with completion if asked. For any subject followed up by telephone, read the complete CWIS and record the subject's responses accurately. Ensure that the subject has completed the CWIS appropriately. A single valid response should be recorded for each item.

NOTE: subjects who cannot read/write may have the CWIS read aloud to them and the subject's responses recorded. Ensure this process is noted in the source documents.

3. Ask the subject to assess the comfort of wearing the dressing since the last visit (see Section 9.5.8).

4. Assess the movement of the dressing (see Section 9.5.9).

5. Remove the old dressing and inspect the ulcer. Complete an ulcer assessment (see Section 9.5.1).

   ***Notes**: 1) A full ulcer assessment is not necessary if the subject has already been discharged or withdrawn from treatment.*

   2) Not applicable if this visit is completed via a phone call.

6. Assess the level of pain experienced by the subject when the dressing is removed (see Section 9.5.6).

7. Assess the ease of dressing removal, leakage, and absorption under compression (see section 9.5.10)

8. Take a photograph of the ulcer, showing the ruler as supplied. Record any debridement and the method of debridement, and take a photograph of the ulcer immediately prior to and following debridement.

   Photograph the used dressing on both sides, together with any secondary dressing.

   Note: Photographs are not necessary if the subject was discharged or withdrawn from treatment at a previous visit.

9. Redress the ulcer, if clinically indicated, using an appropriate dressing according to group allocation:

   For subjects allocated to the experimental group, apply ALNB as supplied for use in the study, cutting the dressing to size if required and securing with a suitable secondary dressing.

   For subjects allocated to SC apply a suitable protective dressing, other than ALLEVYN LIFE/ALNB.

10. Record details of all dressings used for all subjects, (e.g. brand, size, etc.) as well as any treatment applied underneath the dressing, such as Durafiber or Intrasite gel.

    For subjects randomized to ALNB, record whether or not the dressing was cut to a smaller size.

11. Assess the ease of applying the dressing (see Section 9.5.7), including remains in place and repositioning (if applicable).

12. Instruct the subject to carefully follow the ulcer care instructions until the next dressing change and provide information concerning arrangements for future study visits.

13. Record the total time that the subject spent at the visit (start to finish of ulcer care procedures).

14. If any AE or DevD are observed or reported, they must be recorded as instructed in Section 12 (Adverse Events and Device Deficiencies).

9.2.5 End of Study Visit – Week 12 (84 ± 4 days)

The End of Study Visit will consist of an on-site visit. This should coincide with the normal timing of dressing changes, i.e. seven (7) days or fewer for ALNB.

Subjects who have already had their treatment discontinued/been withdrawn from treatment shall be followed-up either by an on-site visit or by telephone. Obtain information about adverse events and responses to the CWIS.

1. Question subjects regarding any changes in health or concomitant treatment.
2. All subjects must complete the CWIS, including those withdrawn from treatment unless they have been withdrawn from the study.

   Give the subject a printed copy of the CWIS and allow sufficient time for them to complete it. Assist with completion if asked. For any subject followed up by telephone (see above), read the complete CWIS and record the subject's responses accurately. Ensure that the subject has completed the CWIS appropriately. A single valid response should be recorded for each item of the CWIS.

   NOTE: Subjects who cannot read/write may have the CWIS read aloud to them and the subject's responses recorded. Ensure this process is noted in the source documents.
3. Ask the subject to assess the comfort of wearing the dressing since the last visit (see Section 9.5.7).
4. Assess the movement of the dressing (see Section 9.5.9).
5. Remove the old dressing and inspect the ulcer. Complete an ulcer assessment (see Section 9.5.1).

   ***Note**: A full ulcer assessment is not necessary if the subject has already been discharged or withdrawn from treatment.*
6. Assess the level of pain experienced by the subject when the dressing is removed. (see Section 9.5.6).
7. Assess the ease of dressing removal, leakage, and absorption under compression (see section 9.5.10)

8.	Take a photograph of the ulcer, showing the ruler as supplied. Record any debridement and the method of debridement, and take a photograph of the ulcer immediately prior to and following debridement. Photograph the used dressing on both sides, together with any secondary dressing. Note: Photographs are desirable, but not necessary if the subject has been discharged or withdrawn from treatment.
9.	Exit the subject from the study. The subject will be returned to SC and the Investigator will advise him/her of subsequent therapy and/or procedures necessary for their medical condition.
10.	Record the total time that the subject spent at the visit (start to finish of ulcer care procedures).
11.	If any AE or DevD are observed or reported, they must be recorded as instructed in Section 12 (Adverse Events and Device Deficiencies).

9.2.6 Treatment Discontinuation

A subject may be withdrawn from treatment early and discharged from care (see Sections 7.6 and 9.3) prior to follow-up at Visit 2, Visit 3, or the End of Study Visit. However, these subjects will still be retained as active study participants, even though their study treatment has ended. When this occurs, the subject will continue as an active participant for the remainder of the twelve (12) week study period, completing all remaining study visits (either by attending site appointments or by telephone if necessary), to gather complete CWIS data.

1.	Question subjects regarding any changes in health or concomitant treatment.
2.	Give subject given a copy of the CWIS and allow sufficient time for them to complete it. Assist with completion if asked. For any subject followed up by telephone (see above), read the complete CWIS and record the subject's responses accurately. Ensure that the subject has completed the CWIS appropriately. A single valid response should

be recorded for each item of the CWIS.

NOTE: subjects who cannot read/write may have the CWIS read aloud to them and the subject's responses recorded. Ensure this process is noted in the source documents.

3. Ask the subject to assess the comfort of wearing the dressing since the last visit (see Section 9.5.8).

4. Assess the movement of the dressing. (see Section 9.5.9).

5. Remove the old dressing and inspect the ulcer. Complete an ulcer assessment (see Section 9.5.1).

   ***Notes**: 1) A full ulcer assessment is not necessary if the subject has already been discharged or withdrawn from treatment.*

   2) Not applicable if this visit is completed via a phone call.

6. Assess the level of pain experienced by the subject when the dressing is removed. (see Section 9.5.6).

7. Assess the ease of dressing removal, leakage, and absorption under compression (see section 9.5.10).

8. Take a photograph of the ulcer, showing the ruler as supplied. Record any debridement and method of debridement, and take a photograph of the ulcer immediately prior to and after debridement.

   Photograph the used dressing on both sides, together with any secondary dressing.

9. If any AE or DevD are observed or reported, they must be recorded as instructed in Section 12 (Adverse Events and Device Deficiencies).

   Photograph the dressing only if reporting a device deficiency.

10.	Redress the ulcer, if clinically indicated, using an appropriate dressing. Do not apply any dressing supplied by S&N for use within the study, as the study treatment is being discontinued.
11.	Record details of any new dressings applied and complete all remaining items in the eCRF.
12.	Instruct the subject on the need to continue as a participant in the study, providing important information about their health and quality of life, until the End of Study Visit (84 ± 4 days from Visit 1).
13.	If ongoing treatment is clinically indicated, continue to provide the subject with SC for the remainder of the study.
14.	Record the total time that the subject spent at the visit (start to finish of ulcer care procedures).

9.2.7 Unscheduled Visits

Any visits to the research site due to the reference ulcer will be captured as a Routine Dressing Change Visit (Section 9.2.3). Visits to the research site for other reasons may be captured as an Unscheduled Visit at the discretion of the Investigator with all information recorded in the source documents and on the Unscheduled Visit eCRF.

9.2.8 Concomitant Treatment

A concomitant treatment is any drug, substance or device administered at any time from enrollment into the study through the last study visit.

9.2.8.1 *Concomitant Treatments Restricted During the Study*

The following treatments are not permitted:

- Anything under the dressing other than Intrasite or Durafiber.

- Oxidizing agents such as hypochlorite solutions (e.g. EUSOL) or hydrogen peroxide in conjunction with ALNB, as these can reduce the absorbency of the dressing.
- Negative pressure wound therapy

9.2.8.2 *Recording Concomitant Treatments in the eCRF*

Concomitant treatments meeting the following criteria will be recorded on the eCRF:

- All current and past reference ulcer treatments
- Concomitant treatments used to treat the reference ulcer (e.g. systemic antibiotics for a reference ulcer infection) and the peri-ulcer area (such as treatment for erythema, irritation, itching), together with the indication for the medication.
- Concomitant medications used to treat all Serious Adverse Events (SAE), ADE, Serious Adverse Device Effects (SADE) and Unanticipated Adverse Device Effects (UADE).

Adverse device effects related to administration of these treatments must be documented in the appropriate eCRF.

9.3 DISCONTINUED SUBJECTS

Discontinued subjects are those who voluntarily discontinue participation in the study, who are withdrawn from the study for reasons of safety or non-compliance, or who are withdrawn from the study for failure to complete the CWIS at Visit 1. Where possible, the End of Study Visit should be completed for all subjects who discontinue the study early. When consent is withdrawn, the date of and reason for discontinuation should be captured.

Subjects may be discontinued from the study at any time if, in the opinion of the Investigator, their continued participation in the study poses a risk to the subject. Additionally, subjects may be discontinued from the study for the following reasons:

- Adverse device effects
- Lost to follow-up

- Subject decision unrelated to an adverse device effect
- Noncompliance (e.g. did not follow instructions, took disallowed medications, did not communicate with the site staff)
- Other

If appropriate, the Investigator will advise the subject of subsequent therapy and/or procedures necessary for their medical condition, which will consist of SC.

Note that subjects who are withdrawn only from treatment will not automatically discontinue participation in the study, see Section 7.6.

9.4 SUBJECT PREGNANCY

Women of child-bearing potential are not excluded from the study. However, if a woman becomes pregnant during the study, S&N must be contacted immediately. Pregnancy is not reportable as an adverse event; however, complications related to the pregnancy may be reportable as determined on a case-by-case basis. Pregnancy-related information will be collected until the end of the pregnancy.

9.5 STUDY METHODS AND MEASUREMENTS

9.5.1 Ulcer Assessments

Modified Bates-Jensen Wound Assessment Tool

1. **Undermining**: Assess by inserting a cotton-tipped applicator under the wound edge; advance it as far as it will go without using undue force; raise the tip of the applicator so it may be seen or felt on the surface of the skin; mark the surface with a pen; measure the distance from the mark on the skin to the edge of the wound. Continue process around the wound. Then use a transparent metric measuring guide with concentric circles divided into 4 (25%) pie-shaped quadrants to help determine the percent of wound involved.

2. **Necrotic Tissue Type**: Pick the type of necrotic tissue that is predominant in the wound according to color, consistency, and adherence using this guide

White/gray non-viable tissue	=	May appear prior to wound opening; skin surface is white or gray.
Non-adherent, yellow slough	=	Thin, mucinous substance; scattered throughout wound bed; easily separated from wound tissue.
Loosely adherent, yellow slough	=	Thick, stringy, clumps of debris; attached to wound tissue.
Adherent, soft, black eschar	=	Soggy tissue; strongly attached to tissue in center or base of wound.
Firmly adherent, hard/black eschar	=	Firm, crusty tissue; strongly attached to wound base and edges (like a hard scab).

3. **Necrotic Tissue Amount**: Use a transparent metric measuring guide with concentric circles divided into 4 (25%) pie-shaped quadrants to help determine the percent of wound involved.

4. **Exudate Type**: Before assessing exudate type, gently cleanse wound with normal saline. Pick the exudate type that is predominant in the wound according to color and consistency, using this guide:

Bloody	=	Thin, bright red
Serosanguinous	=	Thin, watery pale red to pink
Serous	=	Thin, watery, clear
Purulent	=	Thin or thick, opaque tan to yellow
Foul purulent	=	Thick, opaque yellow to green with offensive odor

5. **Exudate Amount**: Use a transparent metric measuring guide with concentric circles divided into 4 (25%) pie-shaped quadrants to determine the percent of wound area involved with exudate. Use this guide:

None	=	Wound tissues dry.
Scant	=	Wound tissues moist; no measurable exudate.
Small	=	Wound tissues wet; moisture evenly distributed in wound; drainage involves < 25% dressing.
Moderate	=	Wound tissues saturated; drainage may or may not be evenly distributed in wound;

drainage involves > 25% to < 75% dressing.

Large = Wound tissues bathed in fluid; drainage freely expressed; may or may not be evenly distributed in wound; drainage involves > 75% of dressing.

6. **Skin Color Surrounding Wound:** Assess tissues within 4cm of wound edge. Dark-skinned persons show the colors "bright red" and "dark red" as a deepening of normal ethnic skin color or a purple hue. As healing occurs in dark-skinned persons, the new skin is pink and may never darken**.**

7. **Granulation Tissue:** Granulation tissue is the growth of small blood vessels and connective tissue to fill in full thickness wounds. Tissue is healthy when bright, beefy red, shiny and granular with a velvety appearance. Poor vascular supply appears as pale pink or blanched to dull, dusky red color.

8. **Epithelialization:** Epithelialization is the process of epidermal resurfacing and appears as pink or red skin. In partial thickness wounds, it can occur throughout the wound bed as well as from the wound edges. In full thickness wounds, it occurs from the edges only. Use a transparent metric measuring guide with concentric circles divided into 4 (25%) pie-shaped quadrants to help determine the percent of wound involved and to measure the distance the epithelial tissue extends into the wound.

Item	Assessment
1. Undermining	1 = None present 2 = Undermining < 2 cm in any area 3 = Undermining 2-4 cm involving < 50% wound margins 4 = Undermining 2-4 cm involving > 50% wound margins 5 = Undermining > 4 cm or Tunneling in any area
2. Necrotic Tissue Type	1 = None visible 2 = White/grey non-viable tissue &/or non-adherent yellow slough 3 = Loosely adherent yellow slough 4 = Adherent, soft, black eschar 5 = Firmly adherent, hard, black eschar
3. Necrotic Tissue Amount	1 = None visible 2 = < 25% of wound bed covered 3 = 25% to 50% of wound covered 4 = > 50% and < 75% of wound covered 5 = 75% to 100% of wound covered

Item	Assessment
4. Exudate Type	1 = None 2 = Bloody 3 = Serosanguinous: thin, watery, pale red/pink 4 = Serous: thin, watery, clear 5 = Purulent: thin or thick, opaque, tan/yellow, with or without odor
5. Exudate Amount	1 = None, dry wound 2 = Scant, wound moist but no observable exudate 3 = Small 4 = Moderate 5 = Heavy
6. Skin Color Surrounding Wound	1 = Pink or normal for ethnic group 2 = Bright red &/or blanches to touch 3 = White or gray pallor or hypopigmented 4 = Dark red or purple &/or non-blanchable 5 = Black or hyperpigmented
7. Granulation Tissue	1 = Skin intact or partial thickness wound 2 = Bright, beefy red; 75% to 100% of wound filled &/or tissue overgrowth 3 = Bright, beefy red; < 75% & > 25% of wound filled 4 = Pink, &/or dull, dusky red &/or fills < 25% of wound 5 = No granulation tissue present
8. Epithelialization	1 = 100% wound covered, surface intact 2 = 75% to < 100% wound covered &/or epithelial tissue extends to > 0.5 cm into wound bed 3 = 50% to < 75% wound covered &/or epithelial tissue extends to < 0.5 cm into wound bed 4 = 25% to < 50% wound covered 5 = < 25% wound covered

Condition of peri-wound

- Normal
- Erythematous
- Edematous
- Eczematous
- Excoriated
- Macerated

- Indurated

Ulcer length/width/depth

- Using a ruler, obtain the greatest length and width of the ulcer as well as the deepest depth.

Healing status

- Healed (100% re-epithelialized, no drainage, no need for a dressing)
- Not healed

Level of odor

- none
- mild
- moderate
- strong

9.5.2 Photographs

Photograph the ulcer and/or dressing (per visit instructions). Ensure that the paper ruler has the subject number and the date clearly written. The paper ruler should be laid flat next to the ulcer, preferably on the intact skin.

The image should be framed such that the entire reference ulcer/dressing nearly fills the frame. Ensure that identifying information, such as the subject's face, are not visible in the photograph. After obtaining the image, ensure that the image is clear (in focus) and that there is sufficient light to clearly see the ulcer/dressing. Follow sponsor instructions for sending the images to the sponsor.

9.5.3 Ankle Brachial Pressure Index (ABI)

The ABI of each subject must be taken at the initial assessment date, or if there is an ABI result within 30 days of Visit 1 this can be used to confirm eligibility. ABI should be determined per the site's standard procedure.

9.5.4 Biological Samples

This study does not require the collection of any biological samples.

9.5.5 Ulcer Classification

9.5.5.1 *Pressure Ulcers*[8]

Stage 1 Pressure Injury: Non-blanchable erythema of intact skin

Intact skin with a localized area of non-blanchable erythema, which may appear different in darkly pigmented skin. Presence of blanchable erythema or changes in sensation, temperature, or firmness may precede visual changes. Color changes do not include purple or maroon discoloration; these may indicate deep tissue pressure injury.

Stage 2 Pressure Injury: Partial-thickness skin loss with exposed dermis

Partial-thickness loss of skin with exposed dermis. The ulcer bed is viable, pink or red, moist, and may also present as an intact or ruptured serum-filled blister. Adipose (fat) is not visible and deeper tissues are not visible. Granulation tissue, slough, and eschar are not present. These injuries commonly result from adverse microclimate and shear in the skin over the pelvis and shear in the heel. This stage should not be used to describe moisture associated skin damage (MASD) including incontinence associated dermatitis (IAD), intertriginous dermatitis (ITD), medical adhesive-related skin injury (MARSI), or traumatic wounds (skin tears, burns, abrasions).

Stage 3 Pressure Injury: Full-thickness skin loss

Full-thickness loss of skin, in which adipose (fat) is visible in the ulcer and granulation tissue and epibole (rolled wound edges) are often present. Slough and/or eschar may be visible. The depth of tissue damage varies by anatomical location; areas of significant adiposity can develop deep wounds. Undermining and tunneling may occur. Fascia, muscle, tendon, ligament, cartilage and/or bone are not exposed. If slough or eschar obscures the extent of tissue loss this is an Unstageable Pressure Injury.

Stage 4 Pressure Injury: Full-thickness skin and tissue loss

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. Epibole (rolled edges), undermining and/or tunneling often occurs. Depth varies by anatomical location. If slough or eschar obscures the extent of tissue loss this is an Unstageable Pressure Injury.

Unstageable Pressure Injury: Obscured full-thickness skin and tissue loss

Full-thickness skin and tissue loss in which the extent of tissue damage within the ulcer cannot be confirmed because it is obscured by slough or eschar. If slough or eschar is removed, a Stage 3 or Stage 4 pressure injury will be revealed. Stable eschar (i.e. dry, adherent, intact without erythema or fluctuance) on the heel or ischemic limb should not be softened or removed.

9.5.5.2 *Diabetic Foot Ulcers*

Wagner Classification of Diabetic Foot Ulcers

Grade 0: No open lesions; may have deformity or cellulitis

Grade 1: Superficial diabetic ulcer (partial or full thickness)

Grade 2: Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis

Grade 3: Deep ulcer with abscess, osteomyelitis, or joint sepsis

Grade 4: Gangrene localized to portion of forefoot or heel

Grade 5: Extensive gangrenous involvement of the entire foot

9.5.6 Ulcer Pain Scale

The level of pain associated with removing the dressing from the reference ulcer will be assessed at each study visit. The subject will be asked to rate the level of pain when the dressing is removed on a scale of 0 to 10 (no pain to worst pain). The pain measure will be recorded as a whole number only.

9.5.7 Dressing Application

1. How easy was it to apply the dressing?

   Very Easy/Easy/Neither Easy nor Difficult/Difficult/Very Difficult.

   If Difficult or Very Difficult, provide details.

2. Did the dressing stay in place (without assistance) on the ulcer until secondary retention was applied?

   Yes/No

3. Did the dressing need to be repositioned before application of secondary retention?

   Yes/No.

   If yes, was adherence to the ulcer affected after repositioning?

   Yes/No

9.5.8 Dressing Comfort

How comfortable was the dressing to wear?

Very comfortable/Comfortable/Neither Comfortable nor Uncomfortable/Uncomfortable /Very Uncomfortable

If Uncomfortable or Very Uncomfortable, list the reason.

9.5.9 Dressing Movement

Has the dressing moved/shifted since the last visit?

Yes/No

If yes, explain.

9.5.10 Dressing Removal

1. How easy was the dressing to remove?

Very Easy/Easy/Neither Easy nor Difficult/Difficult/Very Difficult

If Difficult or Very Difficult, provide details.

2. Did the dressing leak since the last visit?

Yes/No

3. For VLU under compression, did the dressing absorb exudate since the last visit?

Yes/No

If no, record observation.

9.6 HEALTH-RELATED QUALITY OF LIFE

Changes in subject-reported HRQoL are an important consideration for any post-marketing clinical follow-up study.

This CWIS considers the impact of chronic wounds (leg ulcers and diabetic foot ulcers) on HRQoL, as measured by three domains:

- Physical symptoms and daily living (24 items)

- Social life (14 items)
- Well-being (7 items)

Corresponding scales provide scores between 0 and 100. Each scale has been shown to have good internal consistency, reproducibility, and discriminative validity.

This instrument also includes two further single item 'global' scales for HRQoL and satisfaction with the quality of life. However, their sensitivity and value in detecting change are unclear in reported literature.

subject

10. STATISTICAL DESIGN

There will be a formal Statistical Analysis Plan (SAP); the following is a brief description of the summaries and analyses to be described in this plan.

Unless otherwise stated, all significance tests and hypothesis testing will be two-sided, performed at the 5% significance level. Resulting p-values will be quoted and 95% two-sided confidence intervals will be generated where appropriate. All analyses will be performed in SAS v9.4, or later.

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

10.1 EVALUABILITY

All subjects who provide informed consent are considered study participants. Study populations are defined as follows:

- **Safety population (SAF)**: all subjects who receive study treatment. This population will be used for summaries of disposition of the subjects, protocol deviations/violations, and safety.

- **Full analysis set (FAS):** following the intention to treat principle all randomized subjects who receive study treatment and attend at least one post-baseline assessment will be included. This population will be used for the primary analysis of baseline characteristics, primary variables, secondary variables and exploratory variables.
- **Per protocol (PP) population:** includes all subjects in the FAS population who have no significant protocol deviations, meet the inclusion/exclusion criteria, and did not withdraw early (except for closure at any time). This population will be used for supportive evidence of the primary variable.

10.2 EFFICACY

10.2.1 Primary Efficacy

The primary objective of the study is to compare HRQoL in subjects with chronic wounds. The primary efficacy variable used to measure this objective will be the change from baseline in the CWIS-PSDL scale, over a six week treatment period.

The CWIS-PSDL scale is a 24 item questionnaire split into uses a 5 category Likert scale to answer each item with a 1 - 5 score assigned to each category. The first 12 items focus on whether the subject has experienced any of the items over the past 7 days [Not at all/Not applicable – 5, Seldom – 4, Sometimes – 3, Frequently – 2, Always – 1]. The last 12 items focus on how stressful the experience of the items has been over the past 7 days [Not at all/Not applicable – 5, Slightly – 4, Moderately – 3, Quite a bit – 2, Very applicable – 1]. These scores are then transformed into a 0-100 scale at each time point, where a high score represents a 'good' HRQoL and a low score represents a 'poor' HRQoL, using the following formula:

$$PSDL\ Score = \frac{Sum\ of\ item\ scores - 24}{96} \times 100$$

The increase in CWIS-PSDL score between baseline and 6 weeks will be derived as follows:

$$PSDL\ score\ increase\ =\ (\ Score\ at\ 6\ weeks\ -\ Score\ at\ baseline\ )$$

Subject responses to individual items at each assessment will be summarized as ordinal variables by treatment, wound type (and overall) and level of exudate at baseline.

The CWIS-PSDL score at Baseline and 6 weeks will be summarized as a continuous variable by treatment, wound type (and overall) and level of exudate at baseline.

The increase in CWIS-PSDL score between the Baseline and 6 weeks will be summarized as a continuous variable by treatment, wound type (and overall), baseline mobility, and level of exudate at baseline.

For the primary analysis, an ANCOVA model will be fit to the FAS population with the increase in CWIS-PSDL score between the Baseline and 6 weeks as the dependent variable, treatment (ALNB or SC) and center will be included in the model as fixed effects and subject will be included as a random effect. The covariates for the model to be considered will be wound type, baseline CWIS-PSDL score, baseline exudate level, baseline mobility, and baseline wound area.

The null hypothesis will be that there is no difference between the treatments in the increase from baseline to 6 weeks in the CWIS-PSDL score. An estimate of the LS mean difference between the treatments (ALNB – SC) for the CWIS-PSDL score will be reported, along with the corresponding 95% confidence interval and p-value.

If the assumptions of ANCOVA are not met then a non-parametric analysis will be considered the primary analysis for this variable. A Wilcoxon Rank-Sum test will be used to test for a difference in the increase from baseline score between the two treatments and the Hodges-Lehmann estimate of the median difference will be reported with the corresponding 95% confidence interval.

This analysis will be repeated using the per-protocol population and used as supportive evidence to the primary analysis. Any further sensitivity analyses and discussion of methods of handling missing data will be defined in the SAP.

10.2.2 Secondary Efficacy

Various secondary efficacy variables will also be assessed for differences between the treatment and comparator arms. These are listed below and further details will be included in the SAP.

10.2.2.1 *Key Secondary*

Health-related quality of life (HRQoL)

Subject-reported HRQoL variables (measured using the CWIS) include:

- The increase in CWIS-PSDL scale scores from baseline to three and twelve weeks (separately). This will be analyzed in the same way as described in the primary efficacy analysis.
- Increase from baseline scores to three, six, and twelve weeks will be calculated and analyzed separately in the same way as described in the primary efficacy analysis, for the following variables:
    - CWIS-SL scale
    - CWIS-WB scale
    - CWIS-GQ scale
    - CWIS-SQ scale

10.2.2.2 *Secondary*

Ulcer progression

Ulcer progression variables will be summarized by treatment group at three, six, and twelve weeks.

Part of the assessment of ulcer progression will be done using a modified version of the Bates-Jensen Wound Assessment tool with the following variables being assessed (see section 9.5.1 for the scales used):

- Undermining

- Necrotic tissue type
- Necrotic tissue amount
- Exudate type
- Exudate amount
- Skin color surrounding the wound
- Granulation tissue
- Epithelialization

Other assessments of ulcer progression to be summarized include:

- Condition of peri-wound (categorized as Normal, Erythematous, Edematous, Eczematous, Excoriated, Macerated, Indurated) and the condition of peri-wound at each post-baseline time point cross-tabulated with condition of peri-wound at baseline to be summarized separately.
- Ulcer length/width/depth will be used to derive area and volume. These variables will then be used to derive the reduction in area, depth, and volume from baseline to three, six and twelve weeks. The reduction in each dimension at each assessment will be analyzed as the dependent variable in separate linear regression models. An estimate of the difference between treatments in the reduction from baseline area, depth, and volume (separately) will be reported with the corresponding 95% confidence interval.
- Reference ulcer healed (100% re-epithelialized, no drainage, no need for a dressing) will be summarized at each assessment (at three, six, and twelve weeks) and analyzed using separate logistic regression models with whether the reference ulcer was healed or not at the assessment as the dependent variable.

<u>Healthcare resource use</u>

The following Healthcare resource variables will be summarized by treatment groups and overall at twelve weeks:

- Number and type of dressings used (both primary and secondary dressings), including use of compression therapy
- Number of outpatient visits
- Amount of time in hospital (nights spent as an inpatient)
- Number and type of interventions/procedures including debridement of ulcer (curette, scissors, scalpel, forceps, other)
- Number and type of concomitant therapies/treatments

10.2.3 Exploratory Efficacy

The following exploratory analysis has been planned for three, six, and twelve weeks (unless otherwise stated):

- Dressing wear time (days) will be summarized per subject and overall by treatment group and an estimate of the difference in wear time between treatment groups will be reported with the corresponding 95% confidence interval at twelve weeks only.
- Dressing leakage will be summarized by treatment group and overall
- Ease of dressing application/removal will be summarized by treatment group and overall
- Dressing use (whether dressing was cut and adherence following repositioning) will be summarized by treatment group and overall
- Odor control of dressing will be summarized by treatment group and overall
- Absorption of exudate under compression will be summarized by treatment group and overall
- Reason for dressing change will be summarized by treatment group and overall
- Pain on dressing removal will be summarized by treatment group and overall and an estimate of the difference between treatment groups will be reported with the corresponding 95% confidence interval
- Comfort during wear will be summarized by treatment group and overall

10.3 SAFETY

All safety analyses and summaries will be conducted using the Safety Population. Unless otherwise stated, all safety summaries will be presented by treatment and overall.

Extent of Exposure

The duration of treatment will be summarized.

Adverse Events

Adverse events will be coded and grouped by system organ class using the Dictionary for Medical Drug Regulatory Activities (MedDRA).

The number of subjects reporting: adverse events, serious adverse events, severe adverse events, device-related adverse events, serious device-related adverse events, unexpected adverse events, and serious unexpected adverse events will be summarized. In addition, for each adverse event, the following will be summarized: severity, treatment, the relationship to the investigational device, the possible cause if related, outcome and duration of the resolved adverse events and the duration of the adverse events at trial discontinuation.

The proportion of subjects with a device-related adverse event will be compared between treatments using Fisher's exact test. In addition, the percentage of serious device-related adverse events and the corresponding 1-sided upper 95% confidence limit will be detailed assuming a Poisson distribution for serious device-related adverse events separately for each treatment.

The number and proportion of subjects reporting treatment-emergent adverse events split by treatment separately by system organ class and preferred term will be summarized by:

1. Their relationship with the investigational device (not related or related). If the relationship is missing, the adverse event will be assumed to be treatment-related and a footnote will be added to the table. If a subject experiences more than one preferred term within a system organ class, then the relationship at the system organ class level for that subject will be reported according to their most related relationship for each preferred term.
2. The severity of the adverse event (mild, moderate or severe).

3. Whether or not the adverse event is serious

4. The adverse event outcome.

5. Whether or not the adverse event is expected or unexpected.

11. SAMPLE SIZE JUSTIFICATION

Since there is no previous data upon which to base a sample size calculation, no statistical justification for the sample size is provided. Twenty-five (25) subjects were desired for the ALNB group; a 5:3 randomization ratio was selected so that approximately forty (40) subjects would be enrolled into the study. This number of subjects is based on feasibility only.

12. ADVERSE EVENTS AND DEVICE DEFICIENCIES

12.1 DEFINITIONS

The different categories of adverse events are shown in table 12.1-1 below. The definitions for each of these categories are given in the subsequent sections (see reference within the table).

Table 12.1-1: Categories of Adverse Event

<table>
<tr><th></th><th>NOT DEVICE-RELATED</th><th colspan="2">DEVICE-RELATED</th></tr>
<tr><td>NON-SERIOUS</td><td>ADVERSE EVENT (AE) (SEE 12.1.1)</td><td colspan="2">ADVERSE DEVICE EFFECT (ADE) (SEE 12.1.2)</td></tr>
<tr><td rowspan="3">SERIOUS</td><td rowspan="3">SERIOUS ADVERSE EVENT (SAE) (SEE 12.1.3)</td><td colspan="2">SERIOUS ADVERSE DEVICE EFFECT (SADE) (SEE 12.1.3)</td></tr>
<tr><td>ANTICIPATED</td><td>UNANTICIPATED</td></tr>
<tr><td>ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (ASADE) (SEE 12.1.4)</td><td>UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE) (SEE 12.1.4)</td></tr>
</table>

12.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence temporally associated with the use of an investigational medicinal product or device, whether or not considered causally related to that product/device. An AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease.

AE is used both to refer to AE which are not serious or device related and as an umbrella term referring to adverse events of all classifications.

12.1.2 Adverse Device Effect (ADE)

An Adverse Device Effect (ADE) is an adverse event that, in the opinion of the Investigator, is related to the investigational or comparator device:

- **Not Related** – An AE is considered to be not related to the use of the test article when the effect is DEFINITELY UNRELATED or UNLIKELY to have any relationship to the use of the test article;
- **Related** – An AE is considered to be related to the use of the test article when there is a POSSIBLE, PROBABLE, or DEFINITE relationship between the AE and the use of the test article.

AE related to the use of S&N ancillary products will be reported as ADE.

An ADE is further categorized depending on whether the criteria in section 12.1.3 and 12.1.4 are met.

12.1.3 Seriousness

An AE and an ADE are considered "serious" if, in the view of either the Investigator or the sponsor, it:

- Results in death
- Is life-threatening (*NOTE*: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)
- Requires in subject hospitalization or results in prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Is a medically important event or reaction

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

12.1.4 Anticipated/Unanticipated Serious Adverse Device Effect (ASADE/USADE)

A USADE is a serious ADE that meets any of the above definitions but is also considered, by the Investigator, to be caused by or related to the investigational device, not previously identified in nature, severity or degree in the ALLEVYN LIFE Non-Bordered Instructions for use. An ASADE is a serious ADE that does not meet the criteria for a USADE.

12.1.5 Severity

The severity of every AE will be assessed by the Principal Investigator (PI). AE should be classified as mild, moderate, or severe, regardless of whether or not the AE are considered to be serious or non-serious. The classification should be based on the following definitions:

- **Mild** – An event is mild if the subject is aware of, but can easily tolerate the sign or symptom;
- **Moderate** – An event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities;
- **Severe** – An event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

12.1.6 Device Deficiency (DevD)

A DevD is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. DevD include malfunctions, use errors and inadequate labeling.

12.2 REPORTING PROCEDURES

AE of any kind and DevD will be recorded in the applicable forms, eCRF, and source notes. The Investigator will evaluate all AE for relationship to the device, seriousness, and severity. ADE, SAE, and DevD will be entered into the eCRF and reported to the Sponsor within 24 hours of the Investigator being informed about the event (Figure 12.2-1). Updates to submitted information

will be recorded in the eCRF within 24 hours of the information being available to the Investigator. Ensure that for a device that causes an ADE/DevD, that the device information (Product Name, Product Code, Lot #, Expiration Date, and Size) are entered in the eCRF.

All SAE and ADE will be reviewed by a medically qualified person appointed by the Sponsor to determine which, if any, meet criteria for expedited reporting to the regulatory authorities.

The Investigator will inform the IRB of adverse events according to the IRB requirements.

Figure 12.2-1: Evaluation of an Adverse Event by the Investigator

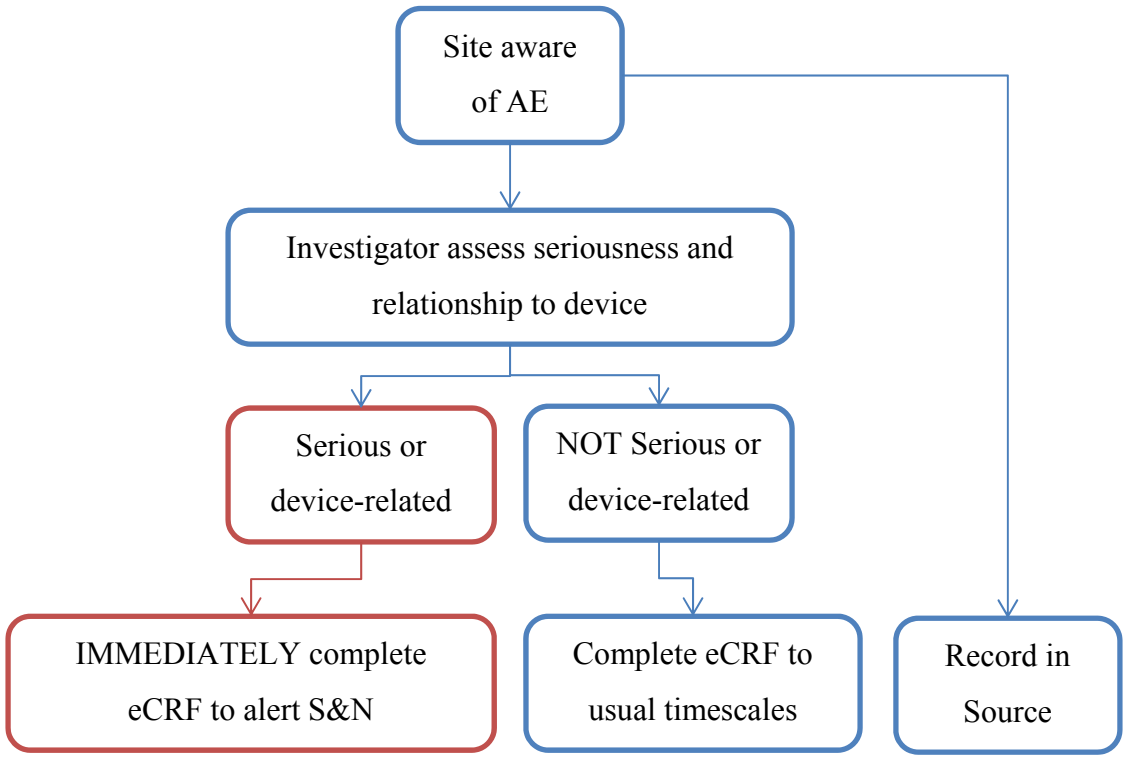


Table 12.2-1: Contact Information for Reporting of Unanticipated Serious Adverse Device Effects

Darrell Lange, PhD Senior Study Manager	Business Phone Mobile Phone email address	817-302-3959 817-707-6219 darrell.lange@smith-nephew.com
Innes Cargill, PhD Medical Monitor	Business Phone Mobile Phone email address	817-302-3913 254-681-1010 innes.cargill@smith-nephew.com

12.3 UNBLINDING OF TEST ARTICLE

Not applicable, as the study is not blinded.

12.4 FOLLOW-UP OF SUBJECTS WITH ADVERSE DEVICE EFFECTS

For subjects who are experiencing ongoing unresolved ADE at the time of their study completion or early discontinuation from the study, it is recommended that the Investigator schedule an appropriate follow-up visit to determine the outcome of the event. Any additional data must be documented and available to the sponsor who will determine whether the data need to be documented within the Clinical Study Report.

13. INVESTIGATOR OBLIGATIONS

The PI will comply with the commitments outlined in the Investigator's Agreement Form provided by the Sponsor, with Good Clinical Practice (GCP), and all applicable regulatory requirements as outlined in Section 21.3 of this protocol.

14. SPONSOR AND MONITOR RESPONSIBILITIES

The Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored to ensure that the rights and wellbeing of the subjects are protected; the reported data are accurate, complete, and verifiable from the

source documents; and the study is conducted in compliance with the currently approved protocol, with current GCP, and with applicable regulatory requirements.

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

15. PROTOCOL AMENDMENTS

Amendments should be made only in exceptional cases once the study has started. Protocol amendments must be approved prior to submission to the IRB. Once approved by the IRB the changes then become part of the protocol.

16. CONFIDENTIALITY OF THE STUDY

The existence of this clinical study is confidential and should not be discussed with persons outside of the study. You shall not use the confidential information for any purpose other than the study. The foregoing obligations of confidence and non-use assumed by you shall not apply to (a) information which at the time of disclosure is in the public domain; (b) information which thereafter lawfully becomes part of the public domain other than through disclosure by or through you; (c) information which, as evidenced by your written records, was known by you prior to S&N's disclosure; (d) information which is lawfully disclosed to you by a third party, not under any obligation of confidence to S&N; or (e) information which is required to be disclosed by law or government regulatory agency, provided reasonable advance notice of such disclosure is given to S&N.

17. STATEMENTS OF COMPLIANCE

This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki; ISO 14155: Clinical investigation of medical devices – Good Clinical Practice[9]; effective for studies commencing after July 1996.

This clinical study will not commence until the required approval/favorable opinion from the IRB or regulatory authority has been obtained. Any additional requirements imposed by the IRB or regulatory authority will be followed.

Public/Products Liability Insurance has been purchased by Smith & Nephew plc. Worldwide and incorporates coverage for personal injury in respect of clinical studies. The Sponsor agrees to operate in good faith the per the ABHI (Association of British Healthcare Industries) guidelines regarding compensation for injury arising in the course of clinical studies.

18. END OF STUDY

The end of the study is defined as the last visit of the last subject undergoing treatment in the study. ALLEVYN LIFE Non-Bordered is a commercially available product and therefore should be available to subjects after their participation in this study. Subjects may participate for a maximum total duration of 88 (84 ± 4) days.

Should circumstances arise which require the termination of the entire study prior to its planned completion (e.g. safety concerns) or circumstances arise which mean the end of the participation of an individual site (e.g. departure of Investigator, non-compliance) then this will be undertaken according to the SOPs of the Sponsor.

19. PUBLICATION POLICY

An analysis of the results of the study submitted by the Investigator will be prepared by the Sponsor in the form of an internal clinical study report. These results are primarily intended for regulatory purposes, rather than external publication. Further details regarding the publication policy for this study can be found in the Clinical Trial Agreement. By signing the Clinical Trial

Agreement the Principal Investigator agrees to comply with the terms and conditions contained therein.

20. REFERENCES

1. Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen. 2009;17:763–71.
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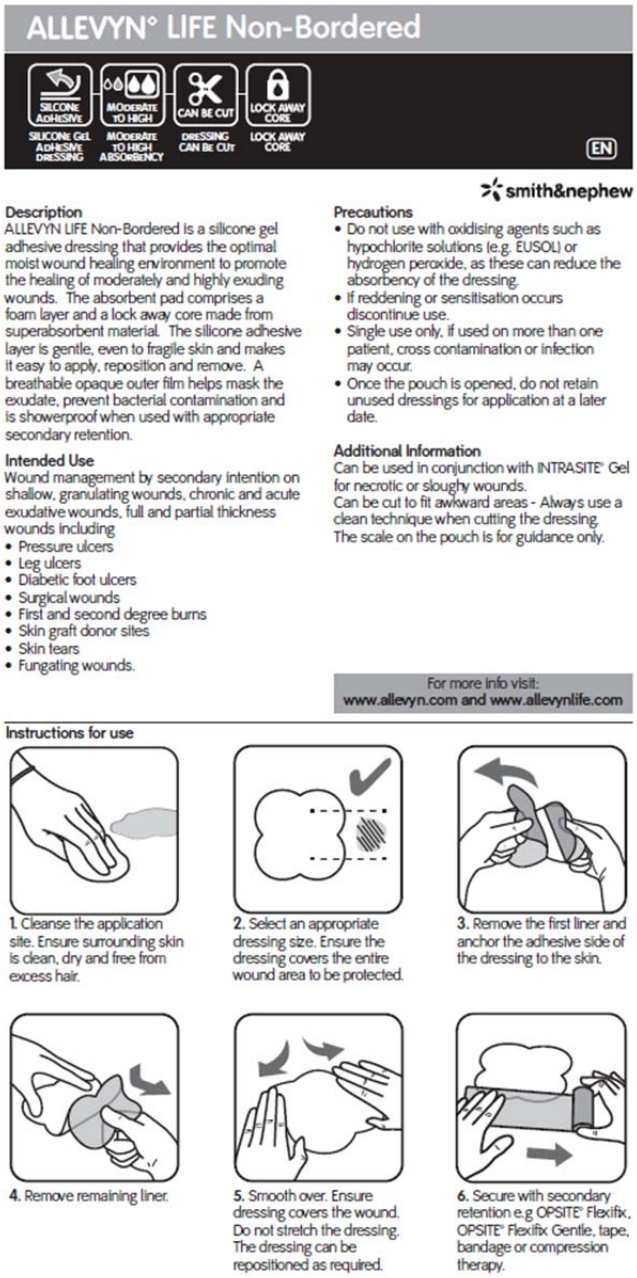
9. ISO 14155:2011 Clinical investigation of medical devices for human subjects – good clinical practice.

21. APPENDICES

21.1 INSTRUCTIONS FOR USE

Revision 9: 24th October 2016



ALLEVYN® LIFE Non-Bordered

SILICONE ADHESIVE — SILICONE GEL ADHESIVE DRESSING
MODERATE TO HIGH — MODERATE TO HIGH ABSORBENCY
CAN BE CUT — DRESSING CAN BE CUT
LOCK AWAY CORE — LOCK AWAY CORE
EN

smith&nephew

Description
ALLEVYN LIFE Non-Bordered is a silicone gel adhesive dressing that provides the optimal moist wound healing environment to promote the healing of moderately and highly exuding wounds. The absorbent pad comprises a foam layer and a lock away core made from superabsorbent material. The silicone adhesive layer is gentle, even to fragile skin and makes it easy to apply, reposition and remove. A breathable opaque outer film helps mask the exudate, prevent bacterial contamination and is showerproof when used with appropriate secondary retention.

Intended Use
Wound management by secondary intention on shallow, granulating wounds, chronic and acute exudative wounds, full and partial thickness wounds including
- Pressure ulcers
- Leg ulcers
- Diabetic foot ulcers
- Surgical wounds
- First and second degree burns
- Skin graft donor sites
- Skin tears
- Fungating wounds.

Precautions
- Do not use with oxidising agents such as hypochlorite solutions (e.g. EUSOL) or hydrogen peroxide, as these can reduce the absorbency of the dressing.
- If reddening or sensitisation occurs discontinue use.
- Single use only, if used on more than one patient, cross contamination or infection may occur.
- Once the pouch is opened, do not retain unused dressings for application at a later date.

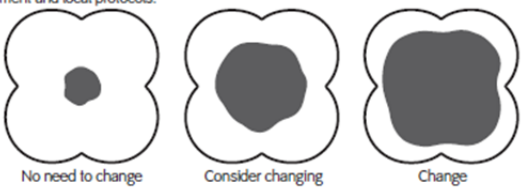
Additional Information
Can be used in conjunction with INTRASITE® Gel for necrotic or sloughy wounds.
Can be cut to fit awkward areas - Always use a clean technique when cutting the dressing.
The scale on the pouch is for guidance only.

For more info visit:
www.allevyn.com and www.allevynlife.com

Instructions for use

1. Cleanse the application site. Ensure surrounding skin is clean, dry and free from excess hair.
2. Select an appropriate dressing size. Ensure the dressing covers the entire wound area to be protected.
3. Remove the first liner and anchor the adhesive side of the dressing to the skin.
4. Remove remaining liner.
5. Smooth over. Ensure dressing covers the wound. Do not stretch the dressing. The dressing can be repositioned as required.
6. Secure with secondary retention e.g OPSITE® Flexifix, OPSITE® Flexifix Gentle, tape, bandage or compression therapy.

Frequency of change
During the early stages of treatment inspect the dressing frequently. Dressings can be left in place for up to 7 days. Dressings should be changed depending on the condition of the wound and surrounding skin or when exudate is within 0.5cm (3/16in) of the dressing edge. The diagram below is for guidance only and the decision of when to change should be dependent upon clinical assessment and local protocols:



No need to change | Consider changing | Change

Removal: Lift one corner and slowly peel back until completely removed.

Product Availability

Code	Size	Availability
66801748	10.5cm x 10.5cm / 4.1in. x 4.1in.	Carton of 10
66801749	16cm x 16cm / 6.3in. x 6.3in.	Carton of 10
66801751	10cm x 20cm / 3.9in. x 7.9in.	Carton of 10

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Ethylene oxide sterilised | Do not use if pack is open or damaged | Do not reuse | Consult instructions for use | Store in a dry place (less than 25°C/77°F) | Caution | Keep away from sunlight

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Wound Healing Research Unit

University of Wales College of Medicine

Cardiff Wound Impact Schedule

Overall Quality of Life

How would you rate your overall quality of life during the past week?

Please circle a number below (Score = number as circled)

How good is your quality of life?

My quality of life is the worst possible	0	1	2	3	4	5	6	7	8	9	10	My quality of life is the best possible

How satisfied are you with your overall quality of life?

Not at all satisfied	0	1	2	3	4	5	6	7	8	9	10	Very satisfied

Overall Comment(s)

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Total

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The following questionnaire is concerned with the effects that your wound has on your daily life. Please answer the questions carefully by placing a tick in the box which most closely reflects how you feel; it should take about ten minutes to complete.

If you are unsure about how to answer a question, please tick the answer which is closest to how you feel. All answers are confidential.

Personal Details

Patient Initials ☐☐☐ **Patient Number** ☐☐☐☐

Date of Birth D D M M Y Y ☐☐ ☐☐ ☐☐

	1st	2nd	3rd	4th	5th
Assessment	☐	☐	☐	☐	☐

Assessment Date ☐☐ ☐☐ ☐☐ **Next Assessment Due** ☐☐ ☐☐ ☐☐

Wound status	Healed	☐	Not Healed	☐
Do you live on your own?	Yes	☐	No	☐

How often do you see your family and friends?

Once a day	☐	Once a month	☐
Once a week	☐	Less than once a month	☐

Social Life

How stressful has this experience been for you?

	Not at all/ Not applicable	Slightly	Moderately	Quite a bit	Very
Difficulty getting out and about	☐	☐	☐	☐	☐
Relying more on others	☐	☐	☐	☐	☐
Your family/friends being over protective	☐	☐	☐	☐	☐
Unable to enjoy your usual social life (eg hobbies)	☐	☐	☐	☐	☐
Limited contact with family/friends	☐	☐	☐	☐	☐
Not going out for fear of bumping your wound site	☐	☐	☐	☐	☐
Wanting to withdraw from people	☐	☐	☐	☐	☐

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For Office Use | Total

Social Life

Have you experienced any of the following during the past week?

	Not at all/ Not applicable	Seldom	Sometimes	Frequently	Always
Difficulty getting out and about	☐	☐	☐	☐	☐
Relying more on others	☐	☐	☐	☐	☐
Your family/friends being over protective	☐	☐	☐	☐	☐
Unable to enjoy your usual social life (eg hobbies)	☐	☐	☐	☐	☐
Limited contact with family/friends	☐	☐	☐	☐	☐
Not going out for fear of bumping your wound site	☐	☐	☐	☐	☐
Wanting to withdraw from people	☐	☐	☐	☐	☐

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Total

Well-being

To what extent do you agree/disagree with the following statements?

	Strongly Disagree	Disagree	Not Sure	Agree	Strongly Agree
I feel anxious about my wound(s)	☐	☐	☐	☐	☐
I feel frustrated at the time it is taking for the wound(s) to heal	☐	☐	☐	☐	☐
I am confident that the wound(s) I have will heal	☐	☐	☐	☐	☐
I worry that I may get another wound in the future	☐	☐	☐	☐	☐
The appearance of the wound site is upsetting	☐	☐	☐	☐	☐
I feel anxious about bumping the wound site	☐	☐	☐	☐	☐
I worry about the impact of the wound(s) on my family/friends	☐	☐	☐	☐	☐

For Office Use

Total

Physical Symptoms and Daily Living

Have you experienced any of the following during the past week?

	Not at all/ Not applicable	Seldom	Sometimes	Frequently	Always
Disturbed sleep	☐	☐	☐	☐	☐
Difficulty in bathing	☐	☐	☐	☐	☐
Immobility around the home	☐	☐	☐	☐	☐
Immobility outside the home	☐	☐	☐	☐	☐
Leakage from the wound	☐	☐	☐	☐	☐
Pain from the wound site	☐	☐	☐	☐	☐
Discomfort from the bandaging/dressing	☐	☐	☐	☐	☐
Unpleasant odour or smell from the wound	☐	☐	☐	☐	☐
Problems with everyday tasks (eg shopping)	☐	☐	☐	☐	☐
Difficulty in finding appropriate footwear	☐	☐	☐	☐	☐
Problems with the amount of time needed to care for the wound site	☐	☐	☐	☐	☐
Financial difficulties as a result of the wound	☐	☐	☐	☐	☐

For Office Use | Total

Physical Symptoms and Daily Living

How stressful has this experience been for you?

	Not at all/ Not applicable	Slightly	Moderately	Quite a bit	Very
Disturbed sleep	☐	☐	☐	☐	☐
Difficulty in bathing	☐	☐	☐	☐	☐
Immobility around the home	☐	☐	☐	☐	☐
Immobility outside the home	☐	☐	☐	☐	☐
Leakage from the wound	☐	☐	☐	☐	☐
Pain from the wound site	☐	☐	☐	☐	☐
Discomfort from the bandaging/dressing	☐	☐	☐	☐	☐
Unpleasant odour or smell from the wound	☐	☐	☐	☐	☐
Problems with everyday tasks (eg shopping)	☐	☐	☐	☐	☐
Difficulty in finding appropriate footwear	☐	☐	☐	☐	☐
Problems with the amount of time needed to care for the wound site	☐	☐	☐	☐	☐
Financial difficulties as a result of the wound	☐	☐	☐	☐	☐

For Office Use | Total

21.3 PRINCIPAL INVESTIGATOR OBLIGATIONS

An Investigator is responsible for:

1. General Responsibilities: [21 CFR §812.100]
   a. Ensuring that an investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations.
   b. Protecting the rights, safety, and welfare of those under the Investigator's care.
   c. The control of devices under investigation.
2. Specific Responsibilities: [21 CFR §812.110]
   a. An Investigator may determine whether potential participants would be interested in participating in an investigation, but shall not request written informed consent of any participant to participate, and shall not allow any participant to participate before obtaining IRB and FDA approval.
   b. An Investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
   c. An Investigator shall permit an investigational device to be used only with participants under the Investigator's supervision. An Investigator shall not supply an investigational device to any person not authorized under this part to receive it.
   d. A clinical Investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The Investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
   e. Upon completion or termination of a clinical investigation or the Investigator's part of an investigation, or at the sponsor's request, an Investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
3. Investigator Records: [21 CFR §812.140(a)]
   a. A participating Investigator shall maintain the following accurate, complete, and current records relating to the Investigator's participation in an investigation:
      i. All correspondence with another Investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
      ii. Record of receipt, use, or disposition of a device that relate to:
         1. The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
         2. The names of all persons who received, used, or disposed of each device.

3. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

b. Records of each participant's case history and exposure to the device. Case histories include case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:
   i. Documents evidencing informed consent and, for any use of a device by the Investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
   ii. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each participant upon entering, and during the course of, the investigation, including information about relevant previous medical history and the result of all diagnostic tests.
   iii. A record of exposure of each participant to the investigational device, including date and time of each use, and any other therapy.

c. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
d. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

4. Retention period: [21 CFR §812.140(d)]
   a. An Investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.
5. Records Custody: [21 CFR §812.140(e)]
   a. An Investigator or sponsor may withdraw from the responsibility to maintain records for the period required in 21 CFR §812.140(d) and transfer custody of the records to any other person who will accept responsibility for them under 21 CFR §812.140, including the requirements of 21 CFR §812.145.
   b. Notice of a transfer shall be given to FDA not later than 10 working days after the transfer occurs.
6. Inspections: [21 CFR §812.145]

a. An Investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, implanted or where records of results from use of devices are kept).
b. An Investigator shall permit authorized FDA employees, at a reasonable time and in a reasonable manner, to inspect and copy all records relating to an investigation.
c. An Investigator shall permit authorized FDA employees to inspect and copy records that identify participants, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the Investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.
d. An Investigator shall prepare and submit the following complete, accurate, and timely reports:
    i. An Investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.
    ii. An Investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the Investigator's part of an investigation.
    iii. An Investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less than yearly.
    iv. An Investigator shall notify the sponsor and the reviewing IRB [21 CFR §56.108(a)(3) and (4)] of any deviation from the investigational plan to protect the life or physical well-being of a participant in an emergency. Such notice shall be given as soon as possible but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human participants, FDA and IRB in accordance 21 CFR §812.35(a) also is required.
    v. If an Investigator uses a device without obtaining informed consent, the Investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
    vi. An Investigator shall, within 3 months after termination or completion of the investigation or the Investigator's part of the investigation, submit a final report to the sponsor and reviewing IRB.

vii. An Investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

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