# STATISTICAL ANALYIS PLAN (SAP)

**Study Details:**

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## 1. List of Abbreviations

| Abbreviation | Definition |
| --- | --- |
| ADE | Adverse Device Effect(s) |
| ADL | Activities of Daily Living |
| AE | Adverse Event(s) |
| ALNB | ALLEVYN™ LIFE Non-Bordered |
| ANOVA | Analysis of Variance |
| ANCOVA | Analysis of Co-Variance |
| BMI | Body Mass Index |
| CRF | Case Report Form(s) |
| CWIS | Cardiff Wound Impact Schedule |
| DevD | Device Deficiency(ies) |
| DFU | Diabetic Foot Ulcer |
| EQ-5D | EuroQol 5D |
| FAS | Full Analysis Set |
| GQ | Global Quality of life |
| HCP | Healthcare Professional |
| HRQoL | Health Related Quality of Life |
| LOCF | Last Observation Carried Forward |
| LU | Leg Ulcer |
| MedDRA | Medical Drug Regulatory Activities |
| PSDL | Physical Symptoms of Daily Living |
| PP | Per-protocol Population |
| PU | Pressure Ulcer |
| QoL | Quality of Life |
| S&N | Smith & Nephew Inc. |
| SADE | Serious Adverse Device Effect(s) |
| SAE | Serious Adverse Event(s) |
| SAP | Statistical Analysis Plan |

| Abbreviation | Definition |
|---|---|
| SAF | Safety Population |
| SC | Standard Care |
| SL | Social Life |
| SQ | Satisfaction with quality of life |
| TFL | Tables, Figures and Listing |
| USADE | Unanticipated Serious Adverse Device Effect(s) |
| VLU | Venous Leg Ulcer |
| WB | Well-being |

## 2. Introduction

The following Statistical Analysis Plan (SAP) details the statistical considerations, including the data analysis methods, for the Study Protocol CT1603ALF. Related documents to this SAP are the Study Protocol, Case Report Form (CRF), and Tables, Figures and Listings (TFLs) Shells.

## 3. Study Design

This is a stratified, randomized, parallel group study. Subjects will be randomly assigned to ALLEVYN™ LIFE Non-Bordered (ALNB) or Standard Care (SC) respectively in a 5:3 ratio. Subjects will be stratified by ulcer type: diabetic foot ulcer (DFU), leg ulcer (LU) and pressure ulcer (PU). 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 3.1 below shows an overview of the study design and table 3.1 shows the planned visit schedule.

**Figure 3.1 – Overview of Study Design**

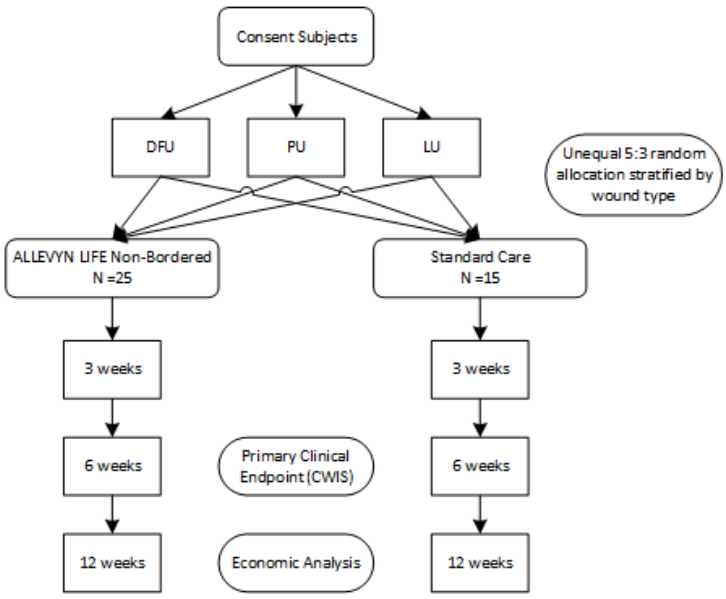

**Table 3.1: Study Visit Schedule**

| 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

## 4. Study Objectives

The overall aim of this pilot randomized controlled trial is to gather preliminary clinical, health economic and safety data on the use of ALNB in the treatment of chronic wounds, for postmarket surveillance and to assist with planning future research concerned with the efficacy and cost-effectiveness of ALNB. The specific objectives are subsequently described.

### 4.1 Primary Objective

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

4.2 Key Secondary Objective

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.

4.3 Secondary Objectives

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

4.4 Exploratory Objective

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

4.5 Safety Objectives

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

- Adverse events
- Device deficiencies

## 5. Study Endpoints

### 5.1 Primary Endpoint

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

### 5.2 Key Secondary Endpoint

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 (Social Life)
- CWIS-WB (Well-being)
- CWIS-GQ (Global Quality of life)
- CWIS-SQ (Satisfaction with quality of life)

CWIS-PSDL will also be compared at 3 and 12 weeks for.

### 5.3 Secondary Endpoints

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

## 5.4 Exploratory Endpoints

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)

5.5 Safety Endpoints

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

- Adverse events
- Device deficiencies

## 6. Statistical Considerations

6.1 Determination of Sample Size

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.

6.2 Randomisation

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

6.3 Interim Analysis

No interim analyses are planned for this study.

## 7. Statistical Analysis

7.1 General

Smith & Nephew's Global Biostatistics group will conduct the statistical analysis for this study. 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 p-values will be

rounded to three decimal places, p-values less than 0.001 will be presented as '<0.001' in all tables.

Where data summaries are specified, categorical and ordinal variables will be summarized with frequencies and percentages. Continuous variables will be summarized with the following summary statistics: number of observations, mean, median, standard deviation, minimum and maximum values. All analyses will be performed in SAS 9.4 (or later).

## 7.2 Analysis Populations

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.

## 7.3 Handling of Missing or Incomplete Data

Cardiff Wound Impact Schedule (CWIS)

If a subject does not have any CWIS data for a post-baseline visit and has at least one post-baseline score then the Last Observation Carried Forward (LOCF) method will be used to carry forward the overall CWIS score.

If a subject is only missing part of the CWIS data at a post-baseline visit, whether that is a full domain or just part of a domain, and has at least one post-baseline score then the LOCF method will be used only for this portion of the CWIS data and the domain scores and overall CWIS score will be calculated again.

For both above instances if the missing data is at the baseline assessment or there are no post-baseline assessments to carry forward then the relevant score will be left as missing.

Modified Bates-Jensen Wound Assessment Tool

If a subject has missing data for the Modified Bates-Jensen Wound Assessment tool and has at least one post-baseline score then the missing data will be handled using the LOCF method. If the missing data is at the baseline assessment or there are no post-baseline assessments to carry forward then the relevant score will be left as missing.

Condition of peri-wound

If a subject has missing data for the condition of the peri-wound and has at least one post-baseline score then the missing data will be handled using the LOCF method. If the missing data is at the baseline assessment or there are no post-baseline assessments to carry forward then the relevant score will be left as missing.

Ulcer dimensions

If a subject has missing data for any values for length, width or depth of the wound at a particular visit, and has at least one post-baseline score, then the LOCF method will be used. The only exception to this is when missing values occur and the ulcer is healed, in which case 0cm (length/ width) or 0mm (depth) shall be imputed for all missing measurements in the statistical analysis.

Ulcer healed status

If the ulcer healed status is missing at a particular assessment and the ulcer was marked as healed at the previous assessment then the ulcer should be classified as healed.
If the ulcer healed status is missing at a particular assessment and the ulcer was not marked as healed at the previous assessment then the ulcer should not be classified as healed. If the baseline ulcer healed status is missing then this should also be implemented as not healed.

In cases where the wound is recorded as healed in the investigators opinion the following imputations will be made if missing values are present: Signs of critical colonisation or infection = No. Level of Exudate = None.

Healthcare resource use

If any of the healthcare resource data is missing then no missing data implementation will be used.

Dressing Change

If any of the dressing change data from the exploratory endpoints is missing then no missing data implementation will be used.

## 7.4 Derived Data

Analysis Populations

- Indicator for inclusion in the safety population.
- Indicator for inclusion in the full analysis set population.
- Indicator for inclusion in the per protocol population.

Demographics, Baseline Data and Disposition Data

- $\text{Age} = (\text{Date of baseline visit} - \text{date of birth}) / 365.25$

  Note: Round down to the nearest whole number.

- Body Mass Index (BMI)$[\mathrm{kg/m^2}] = \text{ weight [lbs]} * 703.07/ (\text{height [inches]})^2$

  Note: the 703.07 is to correct for using pounds and inches.

- Ulcer duration $=$ Date of baseline visit $-$ Date of ulcer onset

- Treatment duration [days] $=$ Date of treatment discontinuaton – date of baseline assessment.

- Duration between visits $=$ Date of Study $\text{Visit}_i$ – date of baseline assessment, where $i = 2,3,4$

- A flag for if the study visit occurs outside of the time range defined in the protocol i.e. Study Visit 2 should occur on Day 21 ± 3 days, Study Visit 3 should occur on Day 42 ± 4 days, End of Study Visit should occur on Day 84 ± 4 days.

  Cardiff Wound Impact Schedule

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

- CWIS SL Score $= \frac{\text{Sum of SL item scores} - 14}{56} * 100$

- CWIS WB Score $= \frac{\text{Sum of WB item scores} - 7}{28} * 100$

- The CWIS-GQ score is the number circled for “How good is your quality of life”

- The CWIS-PQ score is the number circled for “How satisfied are you with your overall quality of life”

- The below formula for individual domain increases from baseline applies to all the above mentioned CWIS domains:

  CWIS domain Score increase $=$ Score at $\text{visit}_i$ $-$ Score at baseline visit, $\quad i = 2,3,4$

Ulcer Progression

- Scoring system for all items of the Modified Bates-Jensen Wound Assessment Tool can be found in the Study Protocol.
- The total Modified Bates-Jensen Score will be calculated by summing the scores from each item.
- If the maximum depth of the wound is marked as superficial then set depth to 0mm.
- $\text{Ulcer area } [\text{cm}^2] = \text{length } [\text{cm}] \text{ x width } [\text{cm}] \text{ x } (\pi/4)$
- $\text{Ulcer volume } [\text{cm}^3] = \text{area } [\text{cm}^2] \text{ x } (\text{depth } [\text{mm}] / 10)$
- For each post-baseline study visit, the percentage reduction ulcer area from baseline assessment will be derived as:

$$\%\text{ reduction in area at Study Visit}_i = \left(\left(\frac{\text{Area}_{\text{SV1}} - \text{Area}_{\text{SVi}}}{\text{Area}_{\text{SV1}}}\right) \times 100\right), \quad i = 2,3,4$$

The same method will be used to derive percentage change in volume and depth.

- For each study visit, the absolute reduction in ulcer area will be derived as:

$$\text{Absolute reduction in ulcer area at Study Visit}_i = \text{Area}_{\text{SV1}} - \text{Area}_{\text{SVi}}, \quad i = 2,3,4$$

The same method will be used to derive percentage change in volume and depth.

Dressing Details

- Dressing wear time (measured in days) will be derived as:

$$\text{Wear time} = \text{Date of dressing removal} - \text{Date of dressing application}$$

- The average wear time over all applications per subject will be derived as follows:

$$\text{Average Wear Time [per subject]} = \frac{\text{Sum of wear time values}}{\text{Count of wear time values}}$$

Adverse Events

- Individual flags for whether each adverse event was a serious adverse event, severe adverse event, investigational device related adverse event, a serious investigational device related adverse event, an unexpected adverse event and a serious unexpected adverse event.
- The duration of adverse events defined as:

  Duration of resolved AE = End date – start date

  Duration of unresolved AE = Date of study completion – start date

7.5 Baseline Data

Demographics

Patient demographics including age, gender, height, weight and body mass index (BMI) will be summarised by treatment group and overall.

Medical History

Relevant medical history (presence/absence of relevant medical conditions), mobility, diabetes status, and type of diabetes will be summarised by treatment group and overall..

Reference Wound Details

Details of the Ulcer type (Pressure Ulcer, Diabetic Foot Ulcer, Venus Leg Ulcer), NPUAP stage (if PU), Wagner Grade (if DFU), Ankle Brachial Pressure Index (if DFU or VLU) Ulcer duration, Ulcer location, whether the wound was debrided at the visit, whether any specific tests related to ulcer performed at the visit and if so what they were, will all be summarised at Baseline by treatment group and overall.

7.6 Disposition Data

The numbers of subjects that are screened, the number of subjects that enter the study and the number of subjects that attend each study visit will be summarised by treatment group and overall.

The reasons for study completion and withdrawal will be summarised by treatment group and overall. The study duration will be summarised by treatment group and overall.

Details of the dates that the first subject was screened, first subject enrolled and the last patient completed will be provided.

7.7 Protocol Deviations

The frequency of protocol deviations and frequency of subjects experiencing each deviation type will summarised by treatment group and overall. This will be done separately for significant deviations, non-significant deviations and all deviations.

7.8 Multiplicity

No adjustments for multiplicity are planned for this study as the study is a pilot with the aim of only collecting data for post-market surveillance and to assist with planning future research.

7.9 Analysis of Primary Endpoint

The primary objective of the study is to compare Health Related Quality of Life (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 using counts and percentages, by treatment (and overall), wound type and amount 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.

Primary Analysis of Primary Endpoint

For the primary analysis an ANCOVA model will be fit to the FAS population with the increase in CWIS-PSDL score between Baseline and 6 weeks as the dependent variable. The model will contain a term for treatment (ALNB or SC) and the following terms will be added to the model using a stepwise selection procedure with an F-value to attain a significance level of 0.1: centre, wound type and BMI, baseline CWIS-PSDL score.

The null hypothesis will be that there is no difference between the treatments in terms of the increase from baseline to 6 weeks in 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. The same analysis will be done as for the parametric analysis however a Rank ANCOVA model will be used instead.

Secondary Analysis of Primary Endpoint

If the data meets the assumptions of using ANCOVA then as a secondary analysis a repeated measures ANCOVA model will be used, with the CWIS-PSDL score as the dependent variable. As a minimum the model will contain terms for treatment, visit and treatment-by-visit interaction. The following terms will be added to the model using a stepwise selection procedure with an F-value to attain a significance level of 0.1: centre, wound type, BMI and baseline CWIS-PSDL score.. P-values for the type III effects in the model will be presented.

Sensitivity Analysis

If LOCF methods are used to account for any missing CWIS-PSDL data at 6 weeks then a sensitivity analysis the same as the primary analysis (ANCOVA model) described above will be carried out on the data treating all missing data as missing with no imputation.

The primary endpoint analysis will be repeated using the per-protocol population (with and without the LOCF imputation).

7.10 Analysis of Key Secondary Endpoints

Health-related quality of life (HRQoL)

The increase in CWIS-PSDL scale scores from baseline to three and twelve weeks (separately) will be analysed in the same way as described in the primary endpoint analysis.

Increase from baseline scores to three, six, and twelve weeks will be calculated and analysed separately in the same way as described in the primary endpoint analysis for the following variables also:

- CWIS-SL scale
- CWIS-WB scale
- CWIS-GQ scale
- CWIS-SQ scale

7.11 Analysis of Secondary Endpoints

Modified Bates- Jensen Wound Assessment Tool

Part of the assessment of ulcer progression will be done using a modified version of the Bates- Jensen Wound Assessment tool assessing: undermining, necrotic tissue type, necrotic tissue amount, exudate type, exudate amount, skin color surrounding the wound, granulation tissue and epithelialization. Each item will be scored according to section 9.5.1 of the study protocol. A total score for each subject at each assessment will be calculated by summing the scores for all 8 items.

The total score for the modified Bates- Jensen Wound Assessment tool will be summarized using descriptive statistics at all visits by treatment and overall. Repeated measures ANCOVA model will be used with the total score as the dependent variable. As a minimum the model will contain terms for treatment, visit and a treatment-by-visit interaction term. The following terms will be added to the model using a stepwise selection procedure with an F-value to attain a significance level of 0.1: centre, wound

type, BMI and baseline CWIS-PSDL score. The difference in least squares mean (LSMean) between treatments at the 3, 6 and 12 week visit will be presented with the associated 95% confidence interval.

Other assessments of ulcer progression

- Condition of peri-wound (categorized as Normal, Erythematous, Edematous, Eczematous, Excoriated, Macerated, Indurated) at each post-baseline time point cross-tabulated with condition of peri-wound at baseline.

- 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 (3, 6 and 12 weeks) will be analysed as the dependent variable in separate ANCOVA models. As a minimum the models will contain a term for treatment. The following terms will be added to the model using a stepwise selection procedure with an F-value to attain a significance level of 0.1: centre, subject, wound type, BMI and the relevant baseline wound dimension (area/ depth/ volume). The estimate difference in the LSMean reductions from baseline in area, depth, and volume (separately) between treatments will be presented with the associated 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 a repeated measures logistic regression model with whether the reference ulcer was healed or not at the assessment as the dependent variable. As a minimum the model will contain a term for treatment. The following terms will be added to the model using a stepwise selection procedure with an F-value to attain a significance level of 0.1: centre, wound type and BMI..

Healthcare resource use

The following Healthcare resource variables will be summarized by treatment groups and overall (i.e. all assessments together) using continuous or categorical data summaries (as appropriate):

- 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

7.12 Analysis of Exploratory Endpoints

- The average dressing wear time (days) per subject will be calculated and this will be summarized as a continuous variable by treatment group and overall. 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
- Durafiber/ Intrasite use will be summarised
- 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

7.13 Analysis of Safety Endpoints

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 by treatment and overall using descriptive summary characteristics for continuous data.

Adverse Events

Adverse events will be coded and grouped by system organ class using a recent version of 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, 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.

The number and proportion of subjects reporting treatment-related adverse, by system organ class and preferred term will be summarized by treatment and overall for:

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 (or worse) relationship for each preferred term.

2. The severity of the adverse event (mild, moderate or severe). If a subject experiences more than one preferred term within a system organ class, then the severity at the system organ class level for that subject will be reported according to their worst severity for each preferred term.

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.

Device deficiencies

The number of device deficiencies and the number of patients reporting a device deficiency will be summarized.

7.14 Other Data Summaries

Not applicable

7.15 Changes in Analysis Methods Specified in the Protocol

The following changes were made to the methods specified in the protocol:

- For the Modified Bates- Jensen Wound Assessment Tool, instead of using a t-test to test for a difference between treatments in the total score at 12 weeks, the repeated measures ANOVA model which was already being used will also be used to

estimate the difference in least squares mean (LSMean) between treatments at the 12 week visit along with associated 95% confidence interval.

- The number of serious device-related adverse events is expected to be low, so it would not be useful to calculate the 1-sided upper 95% CI as originaly planned in the protocol. Instead the number will be summarised and the individual cases will be listed.