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Statistical Analysis Plan

A prospective, multi-center, randomized, open label, parallel-group controlled, non-inferiority trial evaluating the efficacy and safety of the V.A.C. VERAFLO™ Dressing Kit for wound bed preparation in open wounds with extensive soft tissue damage

Author:

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Statistical Analysis Plan Signature Page

Statistical Analysis Plan V3.0 (Dated 02JAN2024) for Protocol KCI.VERAFLO.2018.02. (protocol was amended in 2022 to V2.0)

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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Modification History

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	10JUN2020		Not Applicable – First Version
2.0	09MAY2022		1. Change title of Interim Analysis to Sample Size Re-estimation 2. Change Per Protocol Set to primary analysis set 3. Change Full Analysis Set to secondary analysis set 4. Add Multiple Imputation and NOCB method used to impute missing wound volume and area measures 5. Add sensitivity analysis of primary endpoint (wound volume measure) with Multiple Imputation and NOCB method 6. Add note: If interaction effect is not significant, then it will be removed from the final model 7. Add statistical analysis of imputed secondary endpoint (wound area measure) with LOCF and NOCB method
3.0	02JAN2024		1. Change description of sample size section according to updated protocol. 2. Update the way to report P-value

Table of Contents

1. Introduction

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol KCI.VERAFLO.2018.02. It describes the data to be summarized and analysed, including specifics of statistical analyses to be performed.

This statistical analysis plan (SAP) is based on Protocol KCI.VERAFLO.2018.02., dated 06 September, 2019 (include amended protocol dated 23AUG2022 V2.0).

2. Changes to Planned Analyses as Stated in Protocol

Not applicable.

3. Study Objectives

3.1. Primary Objective

To demonstrate non-inferiority in the wound volume reduction rate of investigational group versus control group patients with open wounds that have extensive soft tissue damage.

3.2. Secondary objectives:

To compare the differences of time to completion of wound bed preparation, wound area reduction rate, wound clinical assessments, incidence of adverse events (AEs) / serious adverse events (SAEs) and device deficiencies in investigational group versus control group.

4. Study Design

4.1. General Description

This is a prospective, multicenter, randomized (1:1), open-label, parallel controlled, non-inferiority trial evaluating the efficacy and safety of V.A.C. VERAFLO™ Dressing Kit versus Negative Pressure Wound Drainage Material (Guangdong Shuangling Pharmaceuticals Co., Ltd.) for wound bed preparation in open wounds with extensive soft tissue damage. This is a pre-marketing trial of V.A.C. VERAFLO™ Dressing Kit in China for National Medical Products Administration (NMPA) registration. It is anticipated that the primary efficacy endpoint (wound volume reduction rate) of investigational group is non-inferior to that of control group. Approximately 140 subjects who meet the eligibility criteria will be randomized to the investigational group or control group at the ratio 1:1.

Debridement is not permitted during study treatment. Therefore, subjects will only be enrolled following definitive surgical debridement (if serial debridements performed) of the target wound. The target wound for each subject in both groups will be treated for up to 14 days or until deemed ready for closure by the investigator (whichever occurs first). Following study treatment, the wound may be treated with any standard therapy selected by the physician, and then accepted secondary intervention for wound closure according to the wound bed preparation situation. The planned study

period consists of the following visits: Screening (Day -3 to 0), Day of randomization (Day0), Dressing change visit(s), End of treatment visit. The following data in both groups will be recorded and collected: wound volume reduction rate, time to completion of wound bed preparation, wound area reduction rate, incidence of AEs / SAEs and device deficiencies. The efficacy and safety of V.A.C. VERAFLO™ Dressing Kit in treating open wounds that have extensive soft tissue damage will be evaluated according to the above data.

4.2. SCHEDULE OF ACTIVITIES

Schedule of events can be found in Section 7.2.2 of the protocol.

5. Planned Analyses

The following analyses will be performed for this study:

- Sample Size Re-estimation
- Final Analysis

5.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC for this study.

5.2. SAMPLE SIZE RE-ESTIMATION

There will be no unblinded interim analysis for this study. A blinded check of the sample size assumptions will take place once at least 70 evaluable subjects have been enrolled.

5.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by Kun Tuo Biostatistics following Sponsor Authorization of this Statistical Analysis Plan and Database Lock.

5.4. SAMPLE SIZE CALCULATION

The number of evaluable subjects required for this trial is 128 subjects (64 per treatment arm). To account for a potential 10% drop-out rate, at least 140 subjects (70 per treatment arm) will be randomly assigned in a 1:1 allocation ratio to V.A.C. VERAFLO™ or control group.

140 evaluable subjects (70 per study arm) will achieve approximately 80% power to detect a difference with a non-inferiority margin of 20% based on a one-sided t test with a significance level of 0.025 and pooled standard deviation being 40%.

Due to the uncertainty in the actual variability and trying to limit the study size to those strictly needed, a sample size re-estimation will be performed after 50% evaluable subjects per arm (70 subjects total) have completed End of Treatment Visit. This number of subjects is expected to provide a sufficiently precise calculation of the variability in the actual study population.

The point estimate for the pooled standard deviation will be used for the sample size re-estimation. If the re-estimated sample size is greater than 140, the sample size may be increased up to a maximum of 200 subjects to provide sufficient power for this study. If the re estimated sample size is less than 140, the sample size of the study is still 140.

Considering the actual drop-out rate during the clinical trial, the drop-out rate needs to be adjusted from the expected 10% to 25%. The sample size will increase by 30 subjects, to a total of maximum 170 subjects.

170 evaluable subjects (85 per study arm) will achieve approximately 80% power to detect a difference with a non-inferiority margin of 20% based on a one-sided t test with a significance level of 0.025 and pooled standard deviation being 40%.

6. ANALYSIS SETS

Agreement and authorization of subjects included/ excluded from each analysis set will be conducted prior to database lock. Prior to the blinded check of the sample size assumptions, the agreement and authorization of subjects excluded/included from the primary dataset (that is, identifying the evaluable subjects) will also be conducted.

6.1. PER PROTOCOL SET (PPS)

PPS is the subset of the FAS, including subjects randomized to receive either VAC VERAFLO or control treatment who do not have major protocol deviations impacting the primary efficacy analysis. It is the primary analysis set for efficacy evaluation.

The rules for exclusion of subjects from the per protocol set (PPS) are as follows:

- Missing baseline volume measure
- Missing end-of-treatment (EOT) volume measure
- Not completing the study (evaluable subjects will have completed the study if deemed ready for closure by investigator or had a treatment duration of up to 14 days*)
- Violating wound size inclusion criterion (maximum depth at baseline < 0.8cm or wound dimensions < 8cm by 1cm) as determined by Independent Assessor (IA)
- Baseline or EOT wound volume measures deemed unreliable after image review (i.e. laser line coverage inadequate, or depth unreliable, or poor margin visibility, or entire wound not imaged, or no comparison across time possible)
- major protocol deviations that would impact the primary endpoint as judged by the medical monitor. For example, post-baseline study wound debridement.

* actual treatment durations of evaluable subjects may be greater than 14 days. Minor protocol deviations should be written for treatment durations outside of the protocol defined window.

There are major PDs defined in the medical monitoring plan (MMD) that do not impact the primary efficacy endpoint. For example, major PDs related to informed consent do not impact the primary efficacy endpoint or interpretation of the primary efficacy analysis.

6.2. FULL ANALYSIS SET (FAS)

Including all subjects who have received either VAC VERAFLO or control treatment. It is the secondary analysis data set for efficacy evaluation. FAS will be analyzed according to the planned treatment group (as randomized).

6.3. SAFETY SET (SS)

Including all subjects who have received either VAC VERAFLO or control treatment. The data set is used to evaluate the safety of this trial. SS will be analyzed according to the actual treatment group.

7. General Considerations

7.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first application of study device with complete date, and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then: Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date then: Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix 1; Partial Date Conventions.

7.2. Baseline

The baseline period will be defined as the period from informed consent to the first study device administration. Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (first dressing application). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

7.3. Retests, Unscheduled Visits and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries.

In the case of a retest (same visit number assigned), the last available measurement for that visit will be used for by-visit summaries.

Early termination data will be mapped to the next available visit number for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

7.4. Windowing Conventions

No visit windowing will be performed for this study

7.5. Statistical Tests

The descriptive statistics of continuous variables include number, mean, standard deviation, median, minimum and maximum. Frequency and percentage will be used in the descriptive statistics for categorical variables. Unless otherwise specified, all statistical tests will be performed at a significance level of 5.0% (two-sided) with two-sided 95% confidence interval (CI).

7.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Treatment Interval X – Baseline Value

7.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.2 or higher.

8. Output Presentations

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by Kun Tuo Biostatistics. All data collected will be listed. When the content of this SAP does not match the template, the template will take priority.

9. Disposition and Withdrawals

All subjects who provide informed consent will be accounted for in this study.

The numbers and percentages of subjects who were randomized, completed and discontinued the study early, as well as the reasons for incompletion, will be summarized by site treatment and overall. The numbers and percentages subjects in each analysis set will be provided by treatment group and overall.

Disposition of all subjects will be listed.

10. Protocol Deviations

Any act of intentional or unintentional variation of the protocol is defined as protocol deviation (PD).
The information of protocol deviation was recorded on the “protocol deviation” CRF page.
Protocol deviations will be summarized by treatment, categories and overall.
The following information will be reported in Full Analysis Set:

- Frequency and percentage of randomized patients with at least one protocol deviation/violation will be summarized by treatment and overall.
- Protocol deviation will be summarized by grade of deviation, treatment group and overall.
- Detailed information of protocol deviations will be listed, including PPS inclusion/exclusion status.

11. Demographic and other Baseline Characteristics

Demographic data and other baseline characteristics will be presented for Full Analysis Set and the Per Protocol Set.

Demographic data and other baseline characteristics will be summarized by treatment and categories, listing will be provided, including PPS inclusion/exclusion status.

Statistical testing will be carried out for demographic or other baseline characteristics (Fisher’s

exact for nominal or ordinal variables, ANOVA for continuous variables).

The following demographic characteristics will be reported for this study:

- Age (years) = (date of consent - date of birth+1)/365.25, and result is rounded down to the nearest integer
- Gender
- Child-bearing potential
- Race
- Ethnicity
- Definitive Surgical Debridement
- Baseline wound area
- Baseline wound area group based on randomization strata (＜15cm^2, 15-30cm^2, and ＞30cm^2)
- Baseline wound volume
- Baseline wound history (wound etiology/type, location, wound age(date of consent - date of wound onset) at the time of consent)

12. Medical History/Wound History

Medical history/Wound History information will be presented for safety set.

The information of medical history inquiry is recorded on the “Medical History Inquiry” CRF page and will be listed and summarized by treatment group and overall.

The following information will be reported for this study:

- Any medical history in the last 3 months(yes/no)
- Serious diabetes medical history(yes/no)
- Surgical history(yes/no)
- Any know allergy in the last 3 months(yes/no)

Pre-existing medical conditions are recorded on the “Medical History” CRF page.

- Medical History will be coded using MedDRA version 22.0.
- Medical History will be listed and summarized by system organ class (SOC) and preferred term (PT).
- If a subject had more than one medical history within a system organ class or Preferred Term, the subject will be counted only once within a system organ class or Preferred Term.

- Medical History conditions are defined as those conditions which stop prior to or at baseline.

Wound history conditions are recorded on the “Wound History” CRF page.

- Wound History for wounds selected for this study will be listed and summarized by wound etiology/type, location, wound age(date of consent - date of wound onset) at the time of consent, Ongoing(Yes/No), Any treatment(Yes/No) and Wound Treatment.

- Wound History conditions are defined as those conditions which stop prior to or at baseline.

13. Medications

Prior and concomitant medications will be presented for safety set, and coded using WHO-Drug DDEB3 201903..

- Concomitant medication will be listed and summarized by Anatomical Therapeutic Chemical (ATC) level 3 and preferred term, a listing will be presented for prior medication. If a subject had more than one concomitant medication within ATC, the subject will be counted only once within a ATC Term.

- Prior medications are medications that started and stopped prior to the first application of study device within the observation.

- Concomitant medications are medications which:

    - Started prior to, on or after the first application of study device within the observation and started no later than the end of the study;
    - AND ended on or after the date of first application of study device within the observation or were ongoing at the end of the study

14. Procedures

The information (frequency and percentage) of prior and concomitant procedures will be summarized by indication, treatment group and overall. When the indication is “AE” or “MH”, the indication will be summarized by SOC and PT.

- Prior procedures are procedures which started and stopped prior to the first application of study device within the observation.

- Concomitant Procedures are Procedures which:

    - Started prior to, on or after the first application of study device within the observation and started no later than the end of the study;
    - AND ended on or after the date of first application of study device within the observation or were ongoing at the end of the study

15. Efficacy Outcomes

PPS is the primary analysis data set for efficacy evaluation. FAS is the secondary analysis set for efficacy evaluation.

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLES & DERIVATIONS

Primary efficacy endpoints

The primary efficacy variable is Wound Volume Reduction Rate, which is wound volume change over 14 days or until deemed ready for closure by investigator (whichever occurred first) ;

Derivations of analysis variables

wound volume reduction rate (unit: %) = (wound volume before initial study treatment –wound volume after study treatment 14 days or deemed ready for closure before 14 days)÷wound volume before initial study treatment×100%.

Data of the variables above will be collected from the CRF.

15.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLES

Subjects in the study whose wound volume reduction rate at effective visit (after study treatment 14 days or deemed ready for closure before 14 days) is unknown will have these missing values imputed in the FAS. Subjects in the PPS will not have any missing values.

The multiple imputation (MI) method will be used to calculate the primary endpoints for each subject for the FAS. The last observation carried forward (LOCF) method and next observation carried back (NOCB) method for missing volume measures will be used to calculate the primary endpoints for each subject for sensitivity analysis using the FAS.

15.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLES

PPS population is the primary efficacy analysis population. Descriptive statistics of actual wound volume, wound volume changes (wound volume before study treatment –wound volume of each visit) and wound volume reduction rate at visit (wound volume before initial study treatment –wound volume at visit)÷wound volume before initial study treatment×100%) by visits, treatment group and overall will be provided.
Listings of actual wound volume will be presented and sorted by subject id, treatment group and visit.

The statistical hypothesis for testing the treatment group difference for primary efficacy endpoint is presented as follows:

- H_0: $M_T - M_C \leq -0.20$ tested against the alternative hypothesis
- H_1: $M_T - M_C > -0.20$

where:
M_C is the means in control group and M_T is the means in to V.A.C. VERAFLO™ group.
A two-sided 95% confidence interval for $M_T - M_C$ will be constructed using the method of ANCOVA with treatment group, center, and treatment-by-center interaction (if the interaction effect is not statistically significant, then it will be removed from the final model) as fixed factors, and wound size (wounds surface area, ＜15cm^2（ref）, 15-30cm^2, and ＞30cm^2) as covariate.
The following statistics will be presented: LS Means, difference of the LS Means as well as its two-sided 95% CI, p-value for LS Mean difference. If the lower limit of the two-sided 95% confidence interval of difference is greater than -0.20, then it will be concluded that the V.A.C. VeraFlo™ Dressing Kit is non-inferior to the approved control dressing in China (Local) + wall suction.
A rejection of the null hypothesis will trigger superiority testing based upon treatment difference. If the lower limit of the CI is greater than zero, V.A.C. VERAFLO™ Dressing Kit is proven to be superior to control dressing.
The two hypothesis tests are hierarchically structured so that the second test (superiority) will only be considered if the first test (non-inferiority) is rejected. There is no alpha adjustment for the second test

as a result of the hierarchical testing.
Furthermore, the following statistics will be presented: P-value of treatment group, center, wound size, and treatment-by-center interaction (present only if interaction effect is significant). If the treatment-by-center interaction in ANCOVA model is significant (<0.025), it always reveals that there is the heterogeneity of substantial treatment in different centers. In order to explain the heterogeneity influence for reliability of statistical conclusion, the descriptive statistics will be reported by different centers.

An example of SAS code is provided:

```
Proc glm;
Class treat woundtypecenter;
Model wound volume reduction rate=treat center treat*center woundtype/ss3;
Lsmean treat/cl pdiff tdiff;
run;
```

15.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

In order to addressing robustness of the primary analysis results of primary efficacy endpoint, several sensitivity analysis approaches are proposed:

- Above statistical analysis method will be conducted using the PPS population.
- Above statistical analysis method will be conducted using the FAS population with multiple imputation (MI) method, last observation carried forward (LOCF) method, and next observation carried back (NOCB) method for primary efficacy endpoint.
- Different statistical models. An analysis of variance (ANCOVA) model on primary efficacy endpoint (wound volume reduction rate) as dependent variables with debridement (occurred before first application or not), treatment group, center, treatment-by-center interaction and treatment-by-wound size interaction (if the interaction effect is not statistically significant, then it will be removed from the final model) as fixed factors, wound size (wounds surface area, $<15cm^2$（ref）, 15-30cm^2, and $>30cm^2$) as covariate will be performed using the PPS population. The following statistics will be presented: LS Means, difference of the LS Means as well as its 95% CI, P-value for LS Mean difference, -value of treatment group, center, treatment-by-center interaction, treatment-by-wound size interaction (present only if interaction effect is significant), debridement and wound size.

15.2. SECONDARY EFFICACY VARIABLES & DERIVATIONS

FAS population will be used for secondary efficacy variables such as the time to completion of wound bed preparation, rate of wound area reduction, and changes in granulation tissue.

15.2.1. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLES

Subjects in the study whose wound area reduction rate at effective visit (after study treatment 14 days or deemed ready for closure before 14 days) is unknown will be imputed. The multiple imputation (MI) method will be used for the FAS analysis, The last observation carried forward (LOCF) method and next observation carried back (NOCB) method will be used to impute missing area measures for each subject as a sensitivity analysis.

Missing value for other secondary endpoints for example time to wound bed preparation will not be imputed and will be treated as missing.

15.2.2. TIME TO COMPLETION OF WOUND BED PREPARATION (UNIT: DAY)

Define: Duration from the randomization until target wound ready for closure by secondary intervention judged by the investigator.
Evaluation time point: Day of Randomization (Day 0) and End of Treatment Visit.
Measurement: the date deemed ready for closure by secondary intervention - the date of the randomization + 1.
Statistical method: the difference between investigational group and control group will be assessed by Kaplan-Meier method and log rank test, and with covariate adjustment using the Cox proportional hazard regression and Wald Chi-Square.

Censor data define: .

The duration of treatment for a patient is considered right-censored if it meets one of the below conditions:

- Patient completed the study but the completion category was “The treatment duration up to 14 Days”, and the subjects’ target wound not ready for closure before end of treatment visit. Patient’s will be censored on day of end of treatment visit.
- Patient prematurely withdraws from the study and the subjects’ target wound not ready for closure before end of treatment visit, patients will be censored on the date of their last 3D wound imaging assessment.
- Subjects with no post-baseline 3D imaging wound measurements assessments will be censored on the day of randomization (i.e. Day 0).

Here, duration of treatment for a patient is defined as the date of the last wound measurements assessments minus the date of randomization plus one.

The Kaplan-Meier analysis of the time to completion of wound bed preparation will be performed, the Kaplan-Meier plot will be presented. The Cox proportional hazard regression with covariates from primary endpoints will be used to estimate the hazard ratios for effect of treatment factor.

The results of the log-rank test for the comparison of investigational group and control groups will be expressed by a Chi-square statistic and P-value, The results of cox proportional hazard regression will be present by HR statistic and P value, the P-value <0.05 will be considered as statistically significant.

An example of SAS code for cox proportion regression model is provided:

```
 Proc phreg;
Class treat(ref=control) center(ref=site1) woundtype(ref=1);
Model time*completion of wound bed preparation(yes) =treat center treat*center woundtype
/risklimite;
Run;
```

Additional analyses will include summary statistics of the number of events and censored values, median time of duration as well as its 95% confidence interval will also be presented. Listings will be presented and sorted by treatment group, subject id.

15.2.3. WOUND AREA REDUCTION RATE (UNIT: %)

Define: wound area change over 14 days or until deemed ready for closure by investigator (whichever occurred first).
Formula: wound area reduction rate = (wound area before study treatment –wound area after study treatment 14 days or deemed ready for closure before 14 days)÷wound area before study treatment×100%.
Measurement: 3D Wound Imaging System, the value for area can be collected from the 3D wound imaging system report directly.

Evaluation time point: Day of Randomization (Day 0), Dressing Change Visit (s), and End of Treatment Visit
Statistical method:
Descriptive statistics of actual wound area and imputed wound area (LOCF and NOCB only) and wound area changes (wound area before study treatment –wound area of each visit) and wound area reduction rate at each visit (wound area before initial study treatment –wound area at each visit)÷wound area before initial study treatment×100%) by treatment group, visits and overall will be provided. Listings of actual wound area and its change will be presented and sorted by subject id, treatment group and visit.

An analysis of covariance (ANCOVA) model on mean change in actual wound area and imputed wound area reduction rate as dependent variables with treatment group, center and treatment-by-center interaction (if the interaction effect is not statistically significant, then it will be removed from the final model) as fixed factors, wound size (wounds surface area, $<15cm^2$ (ref), 15-30cm^2, and $>30cm^2$) as covariate will be performed. The following statistics will be presented: LS Means, difference of the LS Means, as well as its 95% CI, p-value for LS Mean difference, p-value of treatment group, center, treatment-by-center interaction (present only if interaction effect is significant) and wound size. The FAS will be used for this analysis.

15.2.4. WOUND CLINICAL ASSESSMENTS

Define: Wound depth, edges, necrotic tissue type and amount, granulation tissue, undermining, exudate type and exudate amount of target wound after therapy will be evaluated.
Measurement: Wound depth, edges, necrotic tissue type and amount, granulation tissue, undermining, exudate type and exudate amount will be evaluated according to below table.

Wound Depth	1 = non-blanchable erythema on intact skin 2 = Partial thickness skin loss involving epidermis and/or dermis 3 = Full thickness skin loss involving damage or necrosis of subcutaneous tissue; may extend down to but not through underlying fascia; and/or mixed partial and full thickness and/or tissue layers obscured by granulation tissue 4 = Obscured by necrosis 5 = Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures	
Edges	1 = Indistinct, diffuse, none clearly visible 2 = Distinct, outline clearly visible, attached, even with wound base 3 = Well-defined, not attached to wound base 4 = Well-defined, not attached to base, rolled under, thickened 5 = Well-defined, fibrotic, scarred or hyperkeratotic	
Necrotic tissue type	1 = None visible 2 = White/grey non-viable tissue and/or non-adherent yellow slough 3 = Loosely adherent yellow slough 4 = Adherent, soft, black eschar 5 = Firmly adherent, hard, black eschar	
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	
Granulation Tissue	% change in granulation tissue from baseline by 3D Wound Imaging	1 = Skin intact or partial thickness wound 2 = Bright, beefy red; 75% to 100% of wound filled and/or tissue overgrowth 3 = Bright, beefy red; < 75% and > 25% of wound filled 4 = Pink, and/or dull, dusky red and/or fills ~ 25% of

	System	wound 5 = No granulation tissue present
Undermining	1 = None present 2 = Undermining < 2 cm in any area 3 = Undermining 2-4 cm involving s 50% wound margins 4 = Undermining 2-4 cm involving> 50% wound margins 5 = Undermining> 4 cm or Tunneling in any area	
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	
Exudate amount	1 = None, dry wound 2 = Scant, wound moist but no observable exudate 3 = Small 4 = Moderate 5 = Large	

Evaluation time point: Day of Randomization (Day 0), Dressing Change Visit (s), End of Treatment Visit.
Statistical method: The descriptive statistics (frequency and percentage) of wound clinical assessments change from baseline (change scores from -4 to +4) will be summarized by treatment group ,visit and overall. Listings will be presented and sorted by treatment group, subject id.

The Wilcoxon signed rank test and the Wilcoxon rank-sum test will be performed to detect significant changes from baseline within treatment group (p-values) or significant differences in change scores between treatment groups (p-values).

15.3. SUMMARIES FOR WOUND CLOSURE

The wound closure(yes/no), closure method and definitive wound closure method will be summarized by treatment. the information of wound closure will be listed. The chi-square test will be used to test the differences between two groups, p-value will be presented.

15.4. SUMMARIES FOR SUBJECTS RECEIVED TREATMENT

The number of days subjects received treatment and number of dressing changes will be listed and summarized by treatment group. The Wilcoxon rank-sum test will be used to test the differences between two groups, p-value will be presented.

15.5. SUMMARIES FOR NPWT APPLICATION

The application time (minutes) for each dressing change, any leaks and treatment settings will be listed and summarized by treatment group.

16. Exploratory endpoints

An exploratory analysis will be conducted on the exploratory endpoints (volume, area and granulation tissue) using the FAS. Listings will be presented and sorted by treatment group, subject id.

Repeated measure analysis of variance using mixed model on mean change in exploratory endpoints(volume, area and granulation tissue) at each dressing change time point as dependent

variables with center, treatment group and treatment-by-center interaction as fixed factors, wound size (wounds surface area, ＜15cm^2 (ref), 15-30cm^2, and ＞30cm^2) as covariate, and time point as repeated factor will be performed using mixed model. The P-value of center, treatment group, treatment-by-center interaction, wound size and time point will be reported. LS Means and LS Mean difference and P-values for LS Mean difference will be reported out for each visit.

Above statistical analysis method will be conducted on wound area.

An example of SAS code is provided:

```
Proc mixed DATA=xxx covtest metood=ml;
Class id treat center woundtype timepoint;
Model volume(or area,or granulation tissue)=treat center treat*center woundtype timepoint
/htype=3 s noint;
Repeated timepoint/type=sample (covariance structure may be TOFL, AR(1) or UN.  Likelihood
ratio testing (LRT) may be used to select best fitting model
Subject=id(treat);
Run;
```

17. Evaluation of Safety

All outputs for safety outcomes will be based on safety set, and presented by treatment groups.

17.1. Incidence of AEs (unit: %)

Define: an AE is any untoward medical occurrence in the course of a trial, whether or not related to the investigational device.
Evaluation: type, incidence, seriousness and relatedness of AEs/Adverse device effects (ADEs), and laboratory abnormalities will be reported.
Formula: incidence of AEs/ADEs = sum of subject who occurred AEs/ADs ÷sum of subjects for each group×100%.
Statistical method: The incidence of AEs will be summarized by frequency counts along with associated percentages .The Chi square (or Fisher's exact) test will be performed.

17.2. Incidence of SAEs (unit: %)

Define: see relevant subsections of protocol 13.2.1.
Evaluation: incidence, and relatedness of SAEs/Serious adverse device effects (SADEs) will be reported.
Formula: incidence of SAEs/SADEs = sum of subject who occurred SAEs/SADEs ÷sum of subjects for each group×100%.
Statistical method: The incidence of SAEs will be summarized by frequency counts along with associated percentages. The Chi square (or Fisher's exact) test will be performed.

17.3. Incidence of Device deficiencies resulting in AE or SAE (unit: %)

Define: see relevant subsections of protocol 13.3.1.
Formula: incidence of Device deficiencies resulting in AE or SAE = sum of subjects experienced device deficiency resulting in AE or SAE ÷sum of subjects for each group×100%.
Statistical method: The incidence of Device deficiencies resulting in AE or SAE will be summarized by frequency counts along with associated percentages. The Chi square (or Fisher's exact) test will be performed, P-values will be reported.

18. Safety Outcomes

All outputs for safety outcomes will be based on safety set.

There will be no statistical comparison for safety variables of this study.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

18.1. Adverse Events

Adverse Events (AEs) will be coded using MedDRA version 22.0 and presented by System Organ Class (SOC) and Preferred Term (PT). Severity is classed as mild/ moderate/ severe (see protocol 13.1.2 Severity of Event). Safety analyses will be conducted using safety set and by treatment groups.

18.1.1. All Adverse Events

The following AE summaries will be described frequency and percentage by treatment group and overall in an overview summary table:

- AEs
- Severity of AE (mild, moderate, severe)
- Serious AEs
- deaths
- Adverse Device Effect
- Serious Adverse Device Effect
- AEs leading to study termination

If a subject experienced more than one adverse event, the AE with the worst severity will be used in the corresponding summaries.

In addition, all AEs will be listed and presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity of event. If a subject reports an AE more than once within that SOC/ PT, the AE with the worst severity will be used in the corresponding severity summaries.

18.1.2. Adverse Events Leading to Study Termination

AEs leading enrolled subjects removed or withdraw from the study will be listed and statistically described by SOC and PT.

18.1.3. The most common (≥5% incidence) adverse events

The most common(≥5% incidence) adverse events will be listed and presented by SOC, PT and severity.

18.1.4. SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are those events recorded as 'yes' in "Serious" item on the Adverse Events page of the CRF. A listing and summary of SAEs by SOC and PT will be prepared. A summary of SAEs category will be prepared.

18.1.5. ADVERSE DEVICE EFFECT

Relationship, as indicated by the Investigator, is classified as "Unrelated related", "Unlikely related", "Possible related", "Probable related", or "Definitely related". Any AE related to the use of an investigational device is adverse device effect (ADE). A "related" AE is defined as an AE with a relationship to study device as "Definitely related" or "Possible related" or "Probable related". AEs with a missing relationship to study device will be regarded as "Probable related".

Adverse Device Effect will be listed and summarized by SOC, PT and severity.

18.1.6. SERIOUS ADVERSE DEVICE EFFECT

Serious Adverse Device Effect will be listed and summarized by SOC, PT.

18.1.7. ADVERSE EVENTS LEADING TO DEATH

AEs leading to Death are those events which are recorded as 'Yes' or 'Led to death' on the Adverse Events page of the CRF. A listing and summary of AEs leading to death by SOC and PT will be prepared.

18.1.8. DEVICE DEFICIENCY

Device deficiency, device deficiency resulted in an adverse event, and device deficiency resulted in a serious adverse event will be listed separately.

18.2. LABORATORY EVALUATIONS

Laboratory assessment presentations will use SI Units. Laboratory results collected by the CRF will be included in the reporting of this study for Blood Routine Examination, Blood Coagulation Function, and the test items include:

Blood Routine Examination

- Red Blood Cell Count (RBC count,10^9/L)
- Hemoglobin(g/L)
- White Blood Cell count (WBC count, 10^9/L)
- Platelet(10^9/L)

Actual outcomes from the CRF will be listed，the shift from baseline according to markedly abnormal criteria will be provided in order of visit.

Blood Coagulation Function

- Fibrinogen
- Prothrombin Time (PT)

- Activated Partial Thromboplastin Time (APTT)
- International Normalized Ratio (INR)

Actual outcomes from the CRF will be listed.

18.3. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Pulse (bmp)
- Respiratory Rate (Beats/Min)
- Body Temperature(° C)
- Diastolic Blood Pressure(mmHg)
- Systolic Blood Pressure(mmHg)

Actual outcomes from the CRF will be summarized by treatment group and overall. Listing of actual outcomes will be provided.

18.4. PHYSICAL EXAMINATION

The physical examination will be listed and summarized by visits, treatment group and overall.

18.5. PREGNANCY REPORT

Enrolled female will perform following evaluations:

- Pregnancy test (β-HCG),
- Pregnancy information

Actual pregnancy test outcomes and relevant information collected from the CRF will be listed.

APPENDIX 1. **partial date conventions**

Imputed dates will NOT be presented in the listings.

Algorithm for prior / concomitant medications:

Start date	Stop date	Action
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant

Start date	Stop date	Action
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Missing	Assign as concomitant