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Observational Study of the Effect of **V**ar**I**th**E**na® on **W**ound Healing in the Treatment of **V**enous **L**eg **U**lcers Resulting from Chronic Venous Insufficiency (VIEW-VLU)

Statistical Analysis Plan (SAP)

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Statistical Analysis Plan (SAP) Approval Page

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SAP Revision History

Version Number	Date	Brief Description of Changes
1.0	10Dec2018	NA
2.0	08Feb2019	-Updates to window rules per standard of care at sites -Clarification to analysis -Addition of NPRS to Interim Analysis
3.0	12Nov2020	-Provided more clarification on the widnows -Added further clarification on some analyses -Removed subgroup analyses -Removed supportive rate calculation -Removed sensitivity analyses with non-venous vs. venous wounds -Updated NPRS to also use sDCT for analyses -Removed additional analyses for healed vs. non-healed wounds -Removed NPRS category shift table (replaced with numerical shift) -Removed any analyses based on WHI data

Table of Contents

1 Introduction 7
1.1 Study design 7
1.1.1 Sample size 7
1.1.2 Data collection schedule and assessments 8
1.2 Study objectives 9
1.3 Study endpoints 9
2 Changes to protocol analysis 9
3 Statistical methods and analysis 10
3.1 General methodology and definitions 10
3.2 Populations 10
3.3 Disposition, Demographics, Baseline 11
3.3.1 Disposition 11
3.3.2 Demographic and baseline characteristics 11
3.3.3 Protocol deviations 12
3.4 Treatment and other medication and therapies 12
3.4.1 Study treatment 12
3.5 Effectiveness endpoints 13
3.5.1 Primary endpoint(s) 13
3.5.1.1 Rate of epithelial migration (mm/week) by perimeter 13
3.5.1.2 Wound closure at 12 weeks post-treatment 14
3.5.1.3 Time to wound closure 14
3.5.1.4 Missing data handling and other computational rules 14
3.5.2 Secondary endpoints 14
3.5.3.1 Wounds remaining closed at 3 months post-wound closure 14
3.5.3.2 VLU recurrence 14
3.5.3.3 Change in pain on NPRS compared to baseline 14
3.5.3.4 Change on EQ-5D-5L quality of life assessment compared to baseline at 12 weeks and 12 months post-treatment 15
3.5.3.5 Change in VCSS from Baseline to 12 week and 12 month follow-up 15
3.5.3.6 Number of ulcer free weeks (time to recurrence) 16
3.6 Additional Efficacy Analyses 16
3.7 Safety analyses 16
3.8 Interim analysis 16

4 Appendix 18
4.1 EQ-5D-5L Derivations[4] 18
4.2 Demographic Derivations 19
4.3 sDCT data compilation 19
5 Reference 20

List of abbreviations

AASV	Anterior Accessory Saphenous Vein
BMI	Body Mass Index
CEAP	Clinical Etiologic Anatomic Pathophysiologic
CI	Confidence Interval
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EQ-5D-5L	Euroqol five dimension five level questionnaire
FPI	Full Prescribing Information
GSV	Great Saphenous Vein
IFU	Instructions for Use
KM	Kaplan Meier
NPRS	Numeric Pain Rating Scale
SAP	Statistical Analysis Plan
sDCT	Subject Data Capture Tool
SoC	Standard of Care
SSV	Small Saphenous Vein
TLF	Tables, Listings and Figures
VAS	Visual Analogue Scale
VCSS	Venous Clinical Severity Score
VLU	Venous Leg Ulcer
WCC	Wound Care Center
WHI	Wound Health Index

1 Introduction

The statistical analysis plan (SAP) will further describe the analysis outlined in the protocol. The SAP is based on protocol version 1.1 dated 14Aug2017, the electronic case report form (eCRF) version 14.2.2 dated 24Apr2018 and the Tissue Analytics App specifications dated 09Aug2017. A mock-up of tables, listings and figures (TLFs) will be provided in a separate document.

1.1 Study design

This 12 month, multicenter, open-label registry is designed to collect treatment and outcome data related to patients treated with Varithena® for great saphenous vein (GSV) system and/or anterior accessory saphenous vein (AASV) incompetence resulting in venous leg ulcer (VLU). Patients are treated per Investigator's standard of care (SoC) and in accordance with the full prescribing information (FPI) and instructions for use (IFU). For patients with healed ulcers during the 12 month follow-up period, VLU recurrence information is collected. Wound recurrence is defined as the reopening of a wound that was previously closed; all references throughout protocol to wound recurrence refers to wounds that are at the same location.

Note: In cases of cluster wounds, Investigator collects data for a single, primary wound. If more than one wound meets eligibility criteria, Investigator determines which wound to evaluate as the primary/target wound. All endpoint measurements are collected for the primary wound.

For each patient, participation in the registry lasts approximately 12 months. Patients are seen at the investigational site for initial treatment, about one week after treatment for initial follow-up visit (and retreatment if necessary), 12 weeks (±1wk) and 12 months (±1wk) after initial treatment. Between follow-up visits, and until wound closure, patients are asked to collect weekly photographs of the wound via the subject data capture tool (sDCT) during dressing changes at the wound care center (WCC).

Additionally, follow-up phone calls are placed at 3 months (±1wk) post-closure and 6 months (±1 week) post-treatment. At that time, patients are asked to take a picture of the wound area and complete the numeric pain rating scale (NPRS) using the sDCT.

1.1.1 Sample size

No formal statistical hypotheses are being tested and no formal sample size calculation has been performed. The aim of the registry is to collect additional data on treatment effects of a specific indication for which Varithena® is approved but has not been examined in detail. Previous feasibility metrics indicate approximately 200 patients can be enrolled within one year.

1.1.2 Data collection schedule and assessments

Registry Visit	Screening/ Baseline	Enrollment/ Treatment[a] (Day 0)	Week 1 Follow-Up Visit[b]	Week 2 through Wound Closure (at WCC) Weekly	Week 12 (±1wk) Follow-Up Visit	3 Months (±1wk) Post-Closure (phone call)	6 Month (±1wk) Follow-Up (phone call)	Month 12 (±1wk) Follow-Up Visit
Informed consent	X							
Duplex ultrasound of superficial and deep veins	X		X (as necessary)					
Screening: eligibility criteria	X							
Demographics, comorbidities, wound history	X							
Wound Characteristics		X[c]						
Varithena® treatment		X	X (as necessary)[d]					
Hospitalizations for wound?		X	X		X	X	X	X
Patient training to use sDCT			X					
Review of VLU recurrence (if applicable)						X	X	X
Photograph(s) of wound (or closed wound area)	X	X[c]	X[e]	X[e]	X	X[e,f]	X[e,f]	X
Numeric Pain Rating Scale		X[c]	X[e]	X[e]	X	X[e,f]	X[e,f]	X
VCSS		X[c]			X			X
EQ-5D-5L quality of life assessment		X[c]			X			X

[a]completed within 14 days of Screening/Baseline visit. Screening/Baseline and Enrollment/Treatment visit measurements and evaluations may occur at the same visit if patient is provided adequate time to consider and have all questions answered.
[b]not required within first week; should be scheduled per SoC for first follow-up
[c]should be completed prior to treatment with Varithena®
[d]additional treatment with Varithena® cannot occur sooner than 5 days after index treatment
[e]collected/completed by patient using sDCT
[f]Investigator or designee to request during phone follow- up

1.2 Study objectives

The objectives of this registry are to observe the effects of Varithena® on VLU healing in patients who have the symptoms of chronic venous insufficiency, and to evaluate VLU healing rate, recurrence rate, and patient reported outcomes for Varithena® in C6 disease per Clinical Etiologic Anatomic Pathophysiologic (CEAP) classification.

1.3 Study endpoints

The primary endpoints of the study are:

- Rate of epithelial migration (mm/week) measured by wound perimeter on photograph
- Wound closure at 12 weeks (±1wk) post-treatment
- Time from initial treatment with Varithena® to wound closure

The secondary endpoints of the study are:

- Percent of wounds remaining closed at 3 months (±1wk) post-wound closure date, non-healed wounds are not included in percent calculation
- For healed wounds, rate of VLU recurrence (at same site)
- Change in pain on NPRS compared to baseline at 12 weeks (±1wk), 6 months (±1wk), 12 months (±1wk) post-treatment
- Change on Euroqol five dimension five level questionnaire (EQ-5D-5L) quality of life assessment compared to baseline at 12 weeks (±1wk) and 12 months (±1wk) post-treatment
- Change in Venous Clinical Severity Score (VCSS) from baseline to 12 week (±1wk) and 12 month (±1wk) follow-up
- Number of ulcer-free weeks defined as weeks from time of closure (complete epithelialization is recorded) to date of recurrence (at same site) or last contact if no recurrence (at study completion or withdrawal)

2 Changes to protocol analysis

The interim analyses were expanded to look at hospitalization and safety information. Please see section 3.8 for further details.

Additional exploratory analyses from the Wound Health Index (WHI) will not be conducted.

NPRS analyses will use data from both the sDCT and the electronic data capture (EDC). The analysis will be summarized by each week through 12 weeks, 6 months and 12 months post-treatment. Additionally, the categories by severity will not be summarized but rather the numerical scale will be summarized and presented in a shift table. Refer to section 3.5.2 for further details.

Sub-group analyses will not be performed. There is not enough data collected for the analyses to be meaningful.

3 Statistical methods and analysis

3.1 General methodology and definitions

Continuous data will be summarized with means, medians, standard deviations, quartiles (25^{th} and 75^{th}), minima and maxima, unless otherwise specified. Categorical data will be summarized with observed counts and percentages for each category; 95% confidence interval (CI) will be calculated using the Clopper-Pearson (1934)[1] or exact method for binary proportions. For time to event variables, the number of patients, number of events, the median and 95% CI of the median, and quartiles will be provided by the Kaplan Meier (KM) method.

Baseline is defined as the last available measurement taken before the first treatment.

Follow up wound image assessments will need to be slotted into the appropriate visit window described in the table below. Days relative to date of first treatment will be calculated as:

Days = Date of assessment – Date of treatment +1

Visit Timepoint	Target Day	Days Relative to Date of Treatment
1 Week	7	≤7
2 Weeks	14	8 to ≤14
3 Weeks	21	15 to ≤21
4 Weeks	28	22 to ≤28
5 Weeks	35	29 to ≤35
6 Weeks	42	36 to ≤42
7 Weeks	49	43 to ≤49
8 Weeks	56	50 to ≤56
9 Weeks	63	57 to ≤63
10 Weeks	70	64 to ≤70
11 Weeks	77	71 to ≤77
12 Weeks	84 to 91	77 to ≤98
6 Month	183	153 to 213
12 Month	365	335 to 395

If any assessment has more than one wound image in the visit timepoint, the worst (largest) value will be used in the analysis. The range in the target day for weeks were used to mark all follow-up visit timepoints appropriately in instances where the sites could have used either weeks or months for the follow-up. Any assessments outside of the window will not be summarized.

3.2 Populations

The Efficacy Population will include all patients who meet all eligibility, are treated with Varithena®, and who have at least one post-treatment primary endpoint assessment. This will be the primary population and all analyses will be performed on the efficacy population.

3.3 Disposition, Demographics, Baseline

3.3.1 Disposition

Patient disposition will be summarized for all patients. The following categories will be summarized:

- Number of patients screened
- Number and percentage of patients in the efficacy population
- Number and percentage of bilateral patients (2 target wounds)
- Number and percentage of patients who discontinued
- Reasons for discontinuation
    - Withdrawn
    - Lost to follow-up
    - Death
    - Study discontinued by sponsor
    - Other
- Duration on study (months)
    - Duration (months) = (earlier date of study exit/death – date of first treatment + 1)/30.4375

Reasons for discontinuation and study exit dates are collected outside of the EDC. The reasons will be mapped into the categories above by clinical and provided to statistical programming for inclusion in summary table.

3.3.2 Demographic and baseline characteristics

Demographic and baseline characteristics are collected at screening. Descriptive summaries will be provided. The number and percentages (categorical variables) and descriptive statistics (continuous variables) will be summarized for the following:

Demographic

- Age (years), age group (≥ 18 to < 65 years, ≥ 65 to < 75 years, ≥75 years)
- Gender (Male, Female)
- Height (m)
- Weight (kg)
- BMI (kg/m^2)
- BMI Category (18.5 to <25, 25 to <30, ≥30)

Refer to section 0 for derivations.

Disease characteristics

- Leg of target wound (Right, left, both)
- Primary ambulatory method (Walks unaided, cane, crutches, walker, roll about, scooter, wheelchair bound, bed bound)
- Take pain medication regularly? (Yes, No)

Additionally, the following information will be summarized for each target wound:

- Received grafting for target wound? (Yes, No)
- Hospitalization for target wound? (Yes, No)
- Duration of compression therapy at baseline on current target wound (weeks)
- Compliance with compression at baseline? (Yes, No)
- Previous procedures/treatments for target wound? (Yes, No)
- If yes to previous procedure/treatment, outcome of previous treatments (Healed, Not healed)
- Whether target wound is circumferential (Yes, No)
- Wound age at first encounter (weeks)
- Total wounds or ulcers
- Number of previous ulcers
- Signs of infection or bioburden indicated by exudate (Yes, No)

Venous characteristics

The following will be summarized for each target wound:

- Duplex reflux (milliseconds)
- GSV incompetence? (Yes, No)
- AASV incompetence? (Yes, No)
- Major perforator incompetence? (Yes, No)
- Small Saphenous Vein (SSV) incompetence? (Yes, No)
- Peripheral arterial disease? (Yes, No)

3.3.3 Protocol deviations

Protocol deviations/violations not related to the informed consent process or eligibility are not required to be reported to Sponsor for this registry. Protocol deviations related to informed consent or eligibility are tracked outside of the electronic data capture and will be provided in an Excel sheet as the source. The number and percentage of patients with protocol deviations will be summarized.

3.4 Treatment and other medication and therapies

3.4.1 Study treatment

The following index treatment analyses will be summarized by target wound:

- Total injection sites
- Volume injected above the knee (mL)
- Volume injected below the knee (mL)

The number of patients with additional treatment will be summarized. Additionally, the number of additional treatments will also be summarized by wound along with the following:

- Leg (Right, left)
- For target wound? (Yes, no)

- Duration (days) from date of first treatment to the start of an additional treatment
    - *Duration (days) = date of additional Varithena treatment – date of first Varithena treatment + 1*
- Total injection sites
- Volume injected above the knee (mL)
- Volume injected below the knee (mL)

The number of additional treatments will be further split into the number of additional Varithena treatments and the number of adjunctive treatments. Adjunctive treatments are defined as the volume above the knee and below the knee are both 0 mL.

The following treatment analyses will be summarized by visit time point:

- Post-procedure duplex ultrasound performed (Yes, No)
- Duration between treatment and post-procedure duplex ultrasound
    - *Duration (days) = Date of post-procedure duplex ultrasound – date of first treatment + 1*
- Occlusion of target/treated vein? (Yes, No, N/A), for those that had a post-procedure duplex
- Compression compliance? (Yes, No)
- Hospitalized for target wound since last contact? (Yes, No)
- If wound previously closed/healed, was there recurrence? (Yes, No, N/A)
- Has previously healed target ulcer reopened? (Yes, No)

3.5 Effectiveness endpoints

3.5.1 Primary endpoint(s)

Summary statistics with 95% CI will be provided for all primary endpoints. The Clopper-Pearson (1934)[1] method will be used for binary proportions (wound closure at 12 weeks post-treatment). Additionally, distribution of time to wound closure will be estimated using the KM method and the 25th percentile, median, and 75th percentile will be presented along with 95% CIs.

3.5.1.1 Rate of epithelial migration (mm/week) by perimeter

Baseline, time point value, change from baseline and percent change from baseline of the wound perimeter will be summarized by visit time points identified in section 3.1.

The wound perimeter will be evaluated for skewness using the Kolmogorov Smirnov test. In the event of significant skewness, the interquartile range will also be reported in addition to the 95% CI.

Additionally, the baseline, time point value, change from baseline and percent change from baseline will be presented for the subset of wounds that healed.

3.5.1.2 Wound closure at 12 weeks post-treatment

The number and percentage of patients with a wound closure at 12 weeks post-treatment will be presented with a 95% CI. This will be derived as any wounds that closed on or prior to the 12 week visit in the EDC.

3.5.1.3 Time to wound closure

Time to wound closure will be summarized by mean, median, standard deviation, quartiles, minimum and maximum. Additionally, the distribution of the time to wound closure will be analyzed by KM methodology. Any wound that was not closed will be censored at the last date on study. The 25th percentile, median and the 75th percentile will be presented along with the 95% CIs using the methodology of Brookmeyer and Crowley (1982)[2] using the log-log standard error. KM rates will be presented for each week with the corresponding 95% CIs using the log-log transformation methodology of Kalbfleisch and Prentice (1980)[3]. Plots of the KM curve will also be provided.

3.5.1.4 Missing data handling and other computational rules

No missing data will be imputed.

3.5.2 Secondary endpoints

Wound image assessments will be slotted into the windows found in section 3.1.

3.5.2.1 Wounds remaining closed at 3 months post-wound closure

Of wounds that healed during the registry, the number and percentage of wounds remaining closed at 3 months post-wound closure will be summarized along with 95% CI.

Any wounds that healed less than 3 months before the end of the registry will be excluded from the analysis.

3.5.2.2 VLU recurrence

Of wounds that healed during the registry, the number and percentage of VLU recurrences will be summarized along with 95% CI.

3.5.2.3 Change in pain on NPRS compared to baseline

An 11-point NPRS is used to assess patient's level of pain. A patient is asked "What was your pain level at the ulcer location over the last 24 hours?" and selects a score between 0 and 10, with 0 meaning no pain and 10 meaning the worst pain.

Summary statistics for each visit time point and change from baseline for NPRS through 12 weeks, 6 months and 12 months post-treatment will be presented with 95% CI. NPRS

assessments from both the EDC and sDCT will be combined and slotted into windows found in section 3.1. If a patient has more than one assessment during a timepoint, the worst (highest) NPRS score will be used.

Additionally, NPRS assessments will be summarized using shift tables by each visit and worst value post baseline.

3.5.2.4 Change on EQ-5D-5L quality of life assessment compared to baseline at 12 weeks and 12 months post-treatment

The EQ-5D-5L is a self-administered questionnaire consisting of 5 questions pertaining to specific health dimensions (mobility, self-care, pain, usually activities and anxiety and depression), and health status rating scale (visual analogue scale [VAS]). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. If a patient has died, the last EQ-5D-5L dimension assessment prior to death will be imputed as extreme problems (coded as 5).

The VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' (Score=100) and 'the worst health you can imagine' (Score = 0). This information can be used as a quantitative measure of health as judged by the individual respondents. If a patient has died, the last EQ-5D-5L VAS assessment prior to death will be imputed as 0.

Each one digit number expressing the level selected for each dimension can be combined into a 5-digit number describing the respondent's health state. For example, the number 11111 represents the respondent not having any problems in all five dimensions. These 5-digit numbers are health states which can be converted to an index value, where 1 represents full health and 0 is equivalent to death. A health state could be considered worse than death and the index values for those states will be less than 0. The index value will be calculated as:

Index Health State = 1 – (Dimension 1 Estimate + Dimension 2 Estimate + Dimension 3 Estimate + Dimension 4 Estimate + Dimension 5 Estimate)

Each dimension estimated is based on the levels chosen for each dimension and can be found in appendix section 4.1.

Summary statistics for each visit time point and change from baseline for the index health state will be presented with 95% CI. There will be no imputation for missing values.

3.5.2.5 Change in VCSS from Baseline to 12 week and 12 month follow-up

VCSS is a clinician rating of severity of chronic venous insufficiency ranging from 0 to 30, where higher scores indicate more severe venous disease. It assesses nine common signs/symptoms of venous disease: skin changes and pigmentation, inflammation and induration, and ulcers (including number, size, and duration). A tenth item assesses compression

compliance. Each item is scored individually on a 0-3 point scale. The revised VCSS clarifies ambiguities in category descriptions and contains an additional category for compression.

Summary statistics for each time point and change from baseline for VCSS total score at 12 weeks and 12 months post-treatment will be presented with 95% CI.

3.5.2.6 Number of ulcer free weeks (time to recurrence)

The number of ulcer free weeks (time between healed wound and recurrence) will be summarized by mean, median, standard deviation, quartiles, minimum and maximum. If a patient's wound healed but did not have a recurrence, the patient will be censored at the last date of study. Additionally, the distribution of the time to recurrence will be analyzed by KM methodology. The 25th percentile, median and the 75th percentile will be presented along with the 95% CIs using the methodology of Brookmeyer and Crowley (1982)[2] using the log-log standard error. KM rates will be presented for each week through 12 weeks with the corresponding 95% CIs using the log-log transformation methodology of Kalbfleisch and Prentice (1980)[3]. Plots of the KM curve will also be provided.

Information for recurrence will be based on data from the EDC.

3.6 Additional Efficacy Analyses

A univariable cox regression model will be presented for the time to wound closure investigating effects of the following factors in a one at a time analysis: patient age, wound age at first encounter (weeks), presence of infection, ambulatory method, wound size at baseline and total wounds/ulcers of any type. The hazard ratio, 95% CI and the p-value will be summarized for each factor. All factors in the univariable models with a two-sided p-value <0.15 will be included in a multivariable analysis to determine the impact of these factors.

The overall VAS and change from baseline will be presented by summary statistics with 95% CI. Additionally, the EQ-5D-5L misery score will be calculated and summarized similarly to the VAS and index health state score. This is calculated by adding the dimensions together. As an example, if the health state is 11111, then misery score would be 5.

3.7 Safety analyses

The number of serious adverse events related to Varithena® will be listed.

3.8 Interim analysis

An interim futility analysis will be performed when approximately 50 – 75 patients have enrolled and completed their 12 week post-treatment follow-up. The futility analysis will look for the following safety concerns:

- Hospitalizations due to target wound
- Serious adverse events related to Varithena®

If the analyses show there is a high safety concern, the study will be stopped.

Additionally, the descriptive summaries for the primary endpoints (see section 3.5.1 for further details on the primary endpoints) and the secondary endpoint of EQ-5D-5L (see section 0) and NPRS (see section 0) will be performed. Information on baseline wound characteristics (see section 3.3.2), treatment history (see section 3.4.1), post-treatment ultrasound and occlusion (see section 3.4.1) will be also be summarized.

4 Appendix

4.1 EQ-5D-5L Derivations[4]

Question	Text	Coded Value
Mobility	No problems/No pain/Not anxious	1
Self-Care	Slight problems/Slight pain/Slightly anxious	2
Usual Activities	Moderate problems/Moderate pain/Moderately anxious	3
Pain/Discomfort	Severe problems/Severe pain/Severely anxious	4
Anxiety/Depression	Unable/Extreme Pain/Extremely anxious	5

The following table will be used in calculating the index value from the 5-digit health state.

Index value *= 1 – (Dimension 1 Estimate + Dimension 2 Estimate + Dimension 3 Estimate + Dimension 4 Estimate + Dimension 5 Estimate)*

The dimension estimates will be taken from the table below. Each estimate corresponds to the level each respondent checked for each dimension. For example, if a patient has a health state of 23245, the following calculation will be used:

1 – (0.096+0.107+0.068+0.318+0.321) = 0.270

Constant		1.000
Mobility	None	0
	Slight	0.096
	Moderate	0.122
	Severe	0.237
	Unable	0.322
Self-care	None	0
	Slight	0.089
	Moderate	0.107
	Severe	0.220
	Unable	0.261
Usual Activities	None	0
	Slight	0.068
	Moderate	0.101
	Severe	0.255
	Unable	0.255
Pain/discomfort	None	0
	Slight	0.060
	Moderate	0.098

	Severe	0.318
	Unable	0.414
Anxiety/depression	None	0
	Slight	0.057
	Moderate	0.123
	Severe	0.299
	Unable	0.321

4.2 Demographic Derivations

$$Height(m) = (\frac{Height\ (in)}{.39370})/100$$

$$Weight(kg) = (\frac{Weight\ (lbs)}{2.2046})$$

$$BMI\ (kg/m2) = (Weight(kg) * Height(m))^2$$

4.3 sDCT data compilation

The sDCT data will be reviewed by an external investigator to ensure wounds are properly documented. This review will occur multiple times and this will need to be compiled together for analyses.

The following steps will be performed:
1. Study_IDs that are not in the format XXX-XXX will be removed
2. Wound photos that were taken after the date of wound closure indicated by the site in the EDC will be removed
3. Only include images where “No Dot Present” = False
4. The reviewed data will be merged with the fill export by Study_ID and Eval_ID and only reviewed records will be kept
5. Only Target_Would Evaluable = “Evaluated” or “Evaluable” will be included. All others will be removed
6. Any patients with multiple wound ID’s that are not bilateral patients will be given to clinical for review and clinical will provide details on how to handle in the analyses.

5 Reference

1 Clopper, C.; Pearson, E. S. The Use of Confidence or Fiducial Limits Illustrated in the Case of Bionomial. Biometrika. 26: 404-413.
2 Brookmeyer, R., Crowley, J. A Confidence Interval for the Median Survival Time. Biometrics, 1982; 38: 29-41
3 Kalbfleisch, JD and Prentice, RL. The Statistical Analysis of Failure Time Data. 1980. New York: John Wiley & Sons.
4 Pickard, A. S. et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. Value Health. 2019.