Statistical Analysis Plan

A Prospective, Multi-Center, Randomized, Parallel-group Study Comparing AMNIOEXCEL Plus Placental Allograft Membrane to Apligraf Bi-layered Skin Substitute and Standard of Care Procedures in the Management of Diabetic Foot Ulcers

Protocol Number: T-AEPDFU-01 (Version 3.0)

Integra LifeSciences Corporation
311 Enterprise Drive
Plainsboro, NJ 08536 USA

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INTEGRA LIFESCIENCES CORPORATION SIGNATURE PAGE

The undersigned have approved this Statistical Analysis Plan for use in this study.

Signature: _____ **Date:** _____
DD/MMM/YYYY

Qian Mao
Director, Biostatistics
Integra LifeSciences Corporation

Signature: _____ **Date:** 19/Jun/2019
DD/MMM/YYYY

Jessica Knowlton
Manager, Clinical Affairs
Integra LifeSciences Corporation

Signature: _____ **Date:** 19 Jun 2019
DD/MMM/YYYY

Andrew Tummon
Director, Clinical Operations
Integra LifeSciences Corporation

REVISION HISTORY TABLE

Version Number #	***Brief summary of updates***	***Date***
Final 1.0	*Final version*	*18-Apr-2019*
Final 2.0	• *Independent photograph review data is not be included in analysis* • *Number of application analysis is added to ad-hoc analyses* • *Ulcer size reduction is added to the ad-hoc analysis* • *Updated 4-week wound closure analysis* • *Rate of wound closure for all subjects and non-healed subjects analysis have been added to ad-hoc analysis*	*18-Jun-2019*

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List of Abbreviations

Abbreviation	Term
AE	Adverse Event
AMNIOEXCEL Plus	AMNIOEXCEL® Plus Placental Allograft Membrane; the investigational product
Apligraf	a living, bi-layered skin substitute; the comparator investigational product
CMH	Cochran–Mantel–Haenszel
DFU(s)	Diabetic foot ulcer(s)
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
ITT	Intention-To-Treat
LOCF	Last Observation Carried Forward
LTFU	Lost-to-Follow-Up
PP	Per-Protocol
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System, a software system for data analysis and report writing. SAS is a group of computer programs that work together to store data values and retrieve them, modify data, compute simple and complex statistical analyses, and create reports.
SOC	Standard of Care
T-AEPDFU-001	Protocol Number

1. Introduction

This document provides a detailed description of the statistical methods and procedures to be implemented during the analysis of the clinical study. The methods and procedures are intended to support the generation of study report, including detailed descriptions of the populations and methodologies, as well as summary tables, listings and graphics.

This statistical analysis plan (SAP) is based on Version 3.0 of the Protocol# T-AEPDFU-001.

2. Study Objectives

2.1. Primary Efficacy Endpoint

The primary objective of this study is to compare outcomes associated with the use of AMNIOEXCEL Plus Placental Allograft Membrane, Apligraf living, bi-layered skin substitute and SOC in the management of DFUs.

2.2. Secondary Efficacy Endpoints

The secondary endpoints include:

- Determine the proportion of subjects in each study arm with complete closure of the study ulcer at or before 12 weeks of treatment.
- Determine the time to complete wound closure in each study arm.
- Determine the rate of wound closure in each study arm.
- Assess medical resource utilization outcomes in each study arm.

2.3. Exploratory Endpoints

- The proportion of subjects in each cohort whose wounds are closed at 4 weeks of treatment.
- The effect of any covariate on the primary endpoint.

2.4. Safety Endpoints

The safety objective of this study is to assess adverse events associated with either of the study treatments and/or all study procedures in the management of DFUs.

3. Study Design

3.1. Overall Design

This is a prospective, multicenter, parallel-group, randomized, three-arm trial designed to assess the proportion of ulcers achieving complete wound closure and confirmed 2 weeks later in a population with adequate arterial circulation, following up to 11 weeks of either AMNIOEXCEL Plus Placental Allograft Membrane with SOC, Apligraf bi-layered skin substitute with SOC, or SOC alone.

Subjects will be randomized 1:1:1 to receive one of the following:

- AMNIOEXCEL Plus Placental Allograft Membrane with SOC
- Apligraf bi-layered skin substitute with SOC
- SOC alone

3.2. Scientific Rationale for Study Design

Prospective, multicenter, randomized studies provide the most objective methods for analyzing the outcomes of multiple treatment groups. The use of a three-cohort study allows simultaneous comparison of the treatment in question utilizing an active comparator and current SOC, the true baseline.

3.3. Justification for Investigational Products/Treatments

While there may be generalizable evidence that all tissue-based allografts outperform SOC therapies in the management of DFUs, the performance of specific products varies. Although there is evidence that AMNIOEXCEL Amniotic Allograft Membrane outperforms SOC procedures, AMNIOEXCEL Plus Placental Allograft Membrane has not been assessed as an advanced wound therapy for DFUs.

The comparator treatment, Apligraf, has been investigated as an advanced treatment for patients with DFUs and has been compared to SOC procedures.

The use of an offloading boot is a known and widely used SOC adjunctive therapy. Clinical studies have shown that offloading with rigid boots provide a more aggressive healing rate as compared to shoes, custom insoles, wheelchairs, bedrest, and/or crutches. The use of a boot in this clinical trial, in addition to moist wound dressings, will provide the most robust baseline to compare the active treatments (i.e., investigational products) against.

3.4. End of Study Definition

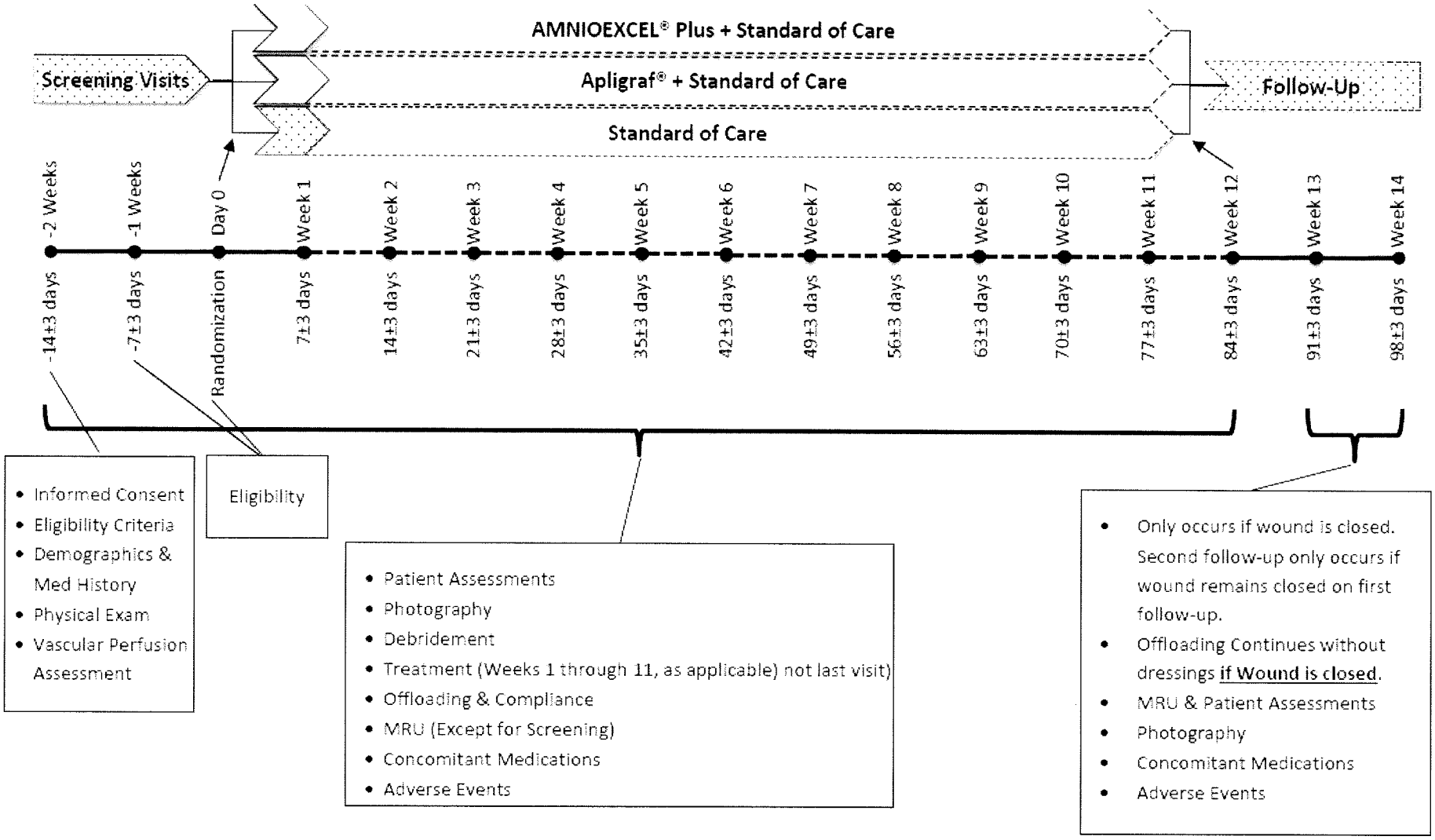
The study is considered completed after all of the screened and enrolled (i.e., randomized) subjects have completed all of their study treatments and been signed off by the investigative sites in the electronic data capture (EDC) system.

4. Study Procedure

The flow chart and schedule for this study are as follows (sections 4.1 and 4.2). Additional information concerning the conduct of the study can be found in the referenced protocol.

4.1. Study Flow Chart

Figure 1: Study Schema



4.2. Schedule of Activities

	Screening		Treatment													Follow-Up Visits		
Procedures (See Section 8 for details)	**Visit 1 -2 Weeks -14±3 days**	**Visit 2 -1 Week -7±3 days**	**Random-ization Day 0**	**Week 1 7±3 days**	**Week 2[a] 14±3 day**	**Week 3[a] 21±3 days**	**Week 4[a] 28±3 days**	**Week 5[a] 35±3 days**	**Week 6[a] 42±3 days**	**Week 7[a] 49±3 days**	**Week 8[a] 56±3 days**	**Week 9[a] 63±3 days**	**Week 10[a] 70±3 days**	**Week 11[a] 77±3 days**	**Week 12[a] 84±3 days**	**Visit 1[b] Week 13 91±3 days**	**Visit 2[b] Week 14 98±3 days**	**Unsched. Visit**
Inf. Consent & HIPAA	X																	
Eligibility Criteria	X	X[c]	X															
Demographics & Medical History	X																	
Physical Examination	X																	
Vascular Perfusion Assessment	X																	
Treatment Compliance Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Debridement[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Photography	X	X	X	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ulcer Assessments[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standard of Care[g]	X	X		X	X	X	X	X	X	X	X	X	X	X				
Boot Application[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X															
Investigational Prod.[i]			X	X[j]	X	X	X	X	X	X	X	X	X	X				X
MRU Assessment				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ConMeds & Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Optional Visit – Conducted if wound is not closed

[b] Optional Visit – Complete ulcer is closed by Week 12. Follow-up visit 2 only occurs if wound remains closed on Follow-up visit 1. Otherwise subject is exited.

[c] Exclusion based on Ulcer Area not applicable at this visit

[d] If Investigator deems it necessary

[e] If subject has been randomized to Apligraf, imaging may not occur at this timepoint. See sections 8.1.2 or 8.2 for detailed instructions.

[f] Study Ulcer Assessments at 1st visit include: 1) location and 2) duration. At each subsequent visit, ulcer area, area reduction, level and type of exudate, presence of signs/symptoms of infection will be made

[g] Weekly *and* daily dressing changes during Screening; Daily continues *only* if randomized to SOC cohort.

[h] Offloading boot required for ulcers on lateral or bottom part of the foot. Boot may be used as a protective device for those subjects with ulcers on the dorsum of the foot

[i] Investigational Product = AMNIOEXCEL Plus or Apligraf is added to SOC Treatment if applicable per randomization, see also footnote *e*.

[j] If Apligraf being used, non-adherent dressing should be left in place on day 7. See Section 6.1 for more information.

5. Sample Size Determination and Rationale

Total of 114 subjects, 38 per cohort, will be enrolled, inclusive with an expected 20% in-study attrition rate.

It is assumed that the maximum wound closure rate is 90% with no difference between the study cohorts. Based on the 38 subject per cohort sample size, the half width of the 95% confidence interval for the wound closure rate is 13.5%. However, the study is not adequately powered for hypothesis testing.

6. Randomization and Blinding

A randomization code has been developed by the Sponsor's Statistical and Data Management teams and have entered it into the EDC system used for data collection. Only these teams will know or have access to these codes and/or the software systems used by the study's investigators. Randomization via the EDC system will only occur on Day 0 of the study after a subject meets all of the inclusion and exclusion criteria set forth in this protocol.

Randomization will be used to minimize bias in this open label study. Randomization will occur in a 1:1:1 ratio and use a mixed block methodology. No blinding is possible. As well, no analytical blinding will occur during data review and/or analysis.

7. Interim Analysis

An interim analysis will occur after 50% of subjects have met the primary endpoint of the study. Descriptive statistics will be provided. Primary and secondary endpoints will be evaluated at the time of interim analysis. There is no hypothesis testing for the interim analysis, and thus no alpha allocation is considered.

8. Analysis Populations

8.1. Intent-to-Treatment Population

The Intent-to-Treat (ITT) population, defined as all randomized subjects who received at least one application of study intervention, will be the primary population for the analysis of primary and secondary efficacy endpoints.

8.2. Per Protocol Population

The Per Protocol (PP) population, defined as all subjects in the ITT population for whom there were no major protocol violation, will be used as supportive for the analyses of the primary and secondary endpoints.

For the per protocol analysis, no data points will be imputed, all missing values will remain as missing.

8.3. Safety Population

The Safety population is defined as all subjects receiving the allocated treatment after randomization. This population will be used for the analysis of safety endpoints.

9. Description of Efficacy Endpoints and Analyses

The primary analysis of the primary efficacy endpoint will be performed using the ITT population. The sensitivity analysis of the primary endpoint will be performed using the PP population. All secondary efficacy endpoints will be performed using the ITT population. Safety analysis will be based on the safety population.

In efficacy or exploratory analyses, covariate analyses will be conducted to assess the impact of various prognostic factors on closure and to demonstrate the robustness of the primary analysis. Prognostic factors (i.e., covariates) will be included if they are found to be contributing factors (i.e., the individual covariate p-value is less than 0.10). Potential prognostic factors to be considered include:

- Ulcer area
- Gender
- Ulcer Location
- Race
- Baseline BMI
- Duration of ulcer
- HbA1c
- Diabetes type
- Nicotine Use

9.1. Primary Endpoint Analysis

The primary endpoint of this study is the incidence of complete wound closure, as assessed by the Investigator at or before Week 12 of the Treatment Phase and confirmed closed 2 weeks later. Confirmed complete wound closure is defined as complete skin re-epithelialization that is without drainage or dressing requirements two weeks later.

A subject is considered to have a closed wound (i.e., a closure success) if the subject's treated wound closes between week 1 and 12 and is noted by the site as closed on both follow-up visits.

A subject is considered to not have a closed wound (i.e., a closure failure) if they meet any of the following:

- the subject's treated wound does not close by week 12
- the subject's treated wound closes between week 1 and 12 and is noted as open on either or both of the follow-up visits.

A subject is considered to have an undetermined wound closure if the subject's treated wound closes between week 1 and 12 and the subject misses either or both of the follow-up visits. These subjects may become part of extended analyses.

The primary analysis will be conducted on the ITT population. The proportion of subjects with confirmed closed study wound, as assessed by the investigator, will be compared between AMNIOEXCEL Plus and Apligraf, and AMNIOEXCEL Plus and SOC. The proportion of subjects with confirmed complete wound closure will be compared using the Cochran–Mantel–Haenszel (CMH) test and logistic regression.

For the primary efficacy analysis, missing values will be imputed using last observation carried forward (LOCF). The differences in confirmed complete wound closure rate between treatment arms will be summarized along with 95% confidence intervals.

A point estimate of the incidence will be presented along with its associated exact 95% confidence interval based on the binomial distribution for Active Treatment and Control Treatment patients respectively.

The complete wound closure as assessed by the Investigator at the end of the Treatment Phase will be listed for each patient.

In addition, subgroup analyses of the primary endpoint will be performed for age, sex, race, region, and other groupings if appropriate.

9.2. Secondary Endpoint Analysis

The secondary endpoints that will be analyzed as part of this trial are as follows:

- Proportion of subjects with complete closure of the study ulcer at or before Week 12 and confirmed 2 weeks later as assessed by computerized planimetry.

- Proportion of subjects with complete wound closure of the study ulcer at or before Week 12 and confirmed 2 weeks later as assessed by independent, blinded, assessment of photographs.
- The Time to complete wound closure, as assessed by the Investigator.
- The Time to complete wound closure, as assessed by computerized planimetry.
- For those wounds that have closed, the rate of wound closure for each group, as assessed by computerized planimetry.
- Medical resource utilization associated with management of DFU and related complications as determined by a comparison of estimated costs from the presumed billing codes which would have been used for each patient. The summary will be provided by an independent group, results will not be included in this analysis

Proportion of ulcers with complete wound closure during the treatment phase as assessed by planimetry will be compared using Logistic Regression with specified baseline covariates in the model.

Time to complete wound closure will be analyzed using the Log-rank test or Cox Proportional Regression Model. The Kaplan-Meier methods will be used to present the distribution of time to complete wound closure.

Summary statistics will be provided for the rate of wound closure for the two treatment groups.

9.3. Exploratory Endpoint Analysis

Exploratory analyses will be performed to examine wound closure status at Week 4 of Treatment and wound closure status at the 2-week follow-up visit

Proportion of subjects with confirmed complete wound closure of the study ulcer at week 4 Treatment Phase, and at the 2-week follow-up visit as assessed by computerized planimetry for each of the treatment groups will be summarized. A point estimate will be presented along with the exact 95% confidence interval based on the binomial distribution.

Exploratory analysis to identify prognostic factors for predicting complete wound closure may be performed. Prognostic factors (i.e., covariates) will be included if they are found to be contributing factors (i.e., the individual covariate p-value is less than 0.10). Potential prognostic factors to be considered include:

- Ulcer area
- Duration of ulcer

- Gender
- Ulcer Location
- Race
- Baseline BMI
- HbA1c
- Diabetes type
- Nicotine Use

9.4. Ad hoc Analyses

The following ad hoc analyses were designed.

- Number of applications per patient analysis, all wounds, healed, and non-healed wounds by treatment
- % of ulcer size reduction at the last visit of the treatment visit, all wounds, healed, and non-healed by treatment
- For all wounds, and non-healed wounds , the rate of wound closure for each group, as assessed by computerized planimetry by treatment

9.5. Missing Data

For primary efficacy evaluation of data points, the last available observation (LOCF) will be used. In the analyses of using the planimetry data, the last available planimetric value will be used for a discontinued subject. All subjects discontinued during the treatment period and before 100% wound closure during the treatment phase of the study will not be replaced and will be considered treatment failures for evaluating the primary and secondary endpoints.

10. Description of Other Variables and Analyses

10.1. General Statistical Considerations

All study data collected in the eCRF will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.4 or later. Descriptive statistics (e.g., n, mean, standard deviation, median, etc.) will be calculated by treatment group for continuous variables. Frequencies and percentages will be presented by treatment group for categorical variables.

Unless otherwise specified, all testing will be performed using two-sided test at the 0.05 level of significance.

10.2. Study Subjects

10.2.1. Subject Disposition

The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, randomized, completed, and discontinued during the study, as well as the reasons for all post-randomization discontinuations will be summarized by treatment group, for all sites combined and each site separately. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

10.2.2. Discontinuations and Protocol Deviation

Protocol deviations will be identified and listed by study sites based on the definitions and constraints set forth in section 10.1.9 of the protocol.

10.2.3. Demographic and Baseline Characteristics

Demographic data including but not limited to age, race, gender, ethnicity, nicotine use and other baseline characteristics, but not limited to medical and surgical history will be tabulated by treatment and overall. Summarized demographic data will include mean, standard deviation, median, minimum and maximum; as well as analogous summary statistics for presenting diagnosis and other relevant patient characteristic factors.

Physical examination (including vitals) will be performed and data will be summarized using descriptive statistics.

10.3. Concomitant Medications and Medical History

Concomitant Medications and Medical History data will be listed for each subject.

10.4. Ulcer Assessment

Data for below questions will summarized by visit using descriptive statistics

- Ulcer Infection Assessment
- Location of Study Ulcer
- Extent of Ulceration
- Ulcer Infection Assessment
- Investigator Assessment of Wound Closure
- Ulcer Exudate Assessment

- Compliance Assessment

10.5. Ulcer Treatment

Data for below questions will be summarized using descriptive statistics by visit.

- Investigational Product Information
- Investigational Product Outer Dressings
- AMNIOEXCEL® Plus Re-application
- Apligraf® Re-application
- Sharp Debridement
- Ulcer Photography
- Standard of Care Treatment,
- Dressing Supplies
- Off-loading Information

10.6. Safety Analysis

Safety will be assessed through reports of adverse events and serious adverse events. Adverse Events related to the device, study ulcer and/or study procedures and all Serious Adverse Events will be recorded.

All safety parameters will be summarized descriptively by treatment. No inferential statistics are planned.

10.7. Adverse Events

Adverse events will be coded using the MedDRA Medical Dictionary. Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the first randomized treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- TEAEs by severity grade
- TEAEs by relationship to study treatment.

In addition, separate summaries of serious adverse events, and adverse events resulting in discontinuation of study treatment will be presented.

The safety population will be used for the safety analyses. Summary will be provided by subject and by adverse events. Subjects will be counted only once for subject-based analysis.

If the same event changes in severity for a subject, the worst severity will be reported. Subjects could be counted more than once for AE-based analysis, all AEs will be reported for AE-based analysis.

An adverse event is considered to be treatment emergent if (1) it was not present when the active phase of the study began, and it is not a chronic condition that is part of the subject's medical history; or (2) it is present at the start of the study or as part of the subject's medical history, but the severity or frequency increased during the active phase. The active phase of the study begins on the day of the first dose of test article and the last dose of test article.

Treatment-emergent adverse events (TEAE) will be summarized for each treatment group by body system and preferred term. The severity of all adverse events will be determined by the investigator's judgment and classified as mild, moderate or severe.

Treatment groups will be compared with respect to the incidence of adverse events (all and TEAEs) and the proportion of subjects withdrawing from the study for adverse events by reason of withdrawal. Comparisons will be made overall, by body system and by preferred term and will be further categorized by severity and by study drug relationship.

10.8. Physical Examination

Data summary will be provided for Physical Examination, including:

- Physical Exam
- Vital Signs
- Vascular Perfusion Assessments
- Multiple DFUs

11. Statistical Methods and Issues

The statistical analysis will be performed by the Clinical Biostatistics Department and/or an approved external vendor.

11.1. Methods of Analysis

11.1.1. Efficacy Endpoints

Confidence interval for proportions:

The method used to compute the two-sided 95% confidence interval (CI) for a single proportion will be the 'exact' method of Clopper and Pearson. For two proportions, the

two-sided 95% CI for the proportion difference will be calculated based on the Z-test with continuity correction.

11.1.2. Standard calculations

The following calculations will be used:

Equation 1. Age of Ulcer

$$Age = int\left(\frac{(date\ of\ ulcer\ at\ baseline - date\ of\ birth + 1)}{365.25}\right)$$

Equation 2. Clinical Trial Duration for a Subject

For subjects completing the study:

2a) $Duration\ (days) = Final\ Follow\ up\ visit\ date - Randomization\ Visit\ Date$

If a subject has not finished treatment (e.g., withdrawals, loss-to-follow-up, etc.)

2b) $Duration_{Withdrawal}(days) = Date\ of\ Withdrawal - Randomization\ Date + 1$

Equation 3. Duration of Adverse Events

$$Duration_{AE} = Onset\ Date_{AE} - Randomization\ Date_{AE} + 1$$

Equation 4. Time to Complete Wound Closure

4a) $Days\ to\ Complete\ Wound\ Closure_{Investigator-based} = (Date\ of\ Last\ Confirmation\ Visit_{EDC}) - (Randomization\ Date) + 1$

Important: This metric will only be calculated for subjects who achieve investigator-based complete wound closure.

EDC: Indicates closure as defined in the EDC system; the investigator-noted closure.

4b) $Days\ to\ Complete\ Wound\ Closure_{Planimetric} = (Date\ of\ Last\ of\ Two\ Successive\ Readings\ of\ 0cm^2{}_{TA}) - (Randomization\ Date) + 1$

Important. Planimetric wound closure will only be calculated for subjects who achieve planimetric-based complete wound closure during the Treatment Phase.

TA: Size from imaging vendor (Tissue Analytics, Inc.) database.

Equation 5. Rate of Wound Closure

$$Rate\ of\ Wound\ Closure\ (\%\ Area/_{Week}) = \frac{7 \times (Area_{baseline} - Area_{final})}{Area_{baseline} \times Duration}$$

Equation 6. Costs Associated with Applied CPT or DRG Codes

6a) $CPT\ Total\ Cost_{Study-Wide} = \sum Estimated\ Costs_{All\ Cohorts}$

6b) $CPT\ Total\ Cost_{Cohort\ X} = \sum Estimated\ Costs_{Cohort\ X}$

6c) $CPT\ Average\ Cost_{Study-Wide} = \frac{\sum Estimated\ Costs_{Study-Wide}}{n_{all\ costs}}$

6d) $CPT\ Average\ Cost_{Cohort\ X} = \frac{\sum Estimated\ Costs_{Cohort\ X}}{n_{cohort-based\ costs}}$

Estimated Costs are based on CPT-10 codes.

Equation 7. Costs Associated with Use of Product

7a) $Cost\ All\ Product_{Study-Wide} = \sum Costs\ Per\ Product_{All\ Cohorts}$

7b) $Cost\ All\ Product_{Cohort\ X} = \sum Costs\ Per\ Product_{Cohort\ X}$

7c) $$Average\ Cost\ All\ Product_{Study-Wide} = \frac{\sum Costs\ Per\ Product_{Study-Wide}}{n_{all\ costs}}$$

7d) $$Average\ Cost\ All\ Product_{Cohort\ X} = \frac{\sum Costs\ Per\ Product_{Cohort\ X}}{n_{cohort-based\ costs}}$$

7e) $$Average\ Cost\ Per\ Week_{Study-Wide} = \frac{\left(\frac{\sum Costs\ Per\ Product_{Study-Wide}}{n_{all\ costs}}\right)}{12}$$

7f) $$Average\ Cost\ Per\ Week_{Cohort\ X} = \frac{\left(\frac{\sum Costs\ Per\ Product_{Cohort\ X}}{n_{cohort-based\ costs}}\right)}{12}$$

Cost of Product is based on (list price? Cost in study?)

Equation 8. Average Applications Per Patient

8a) $$Avg.Applications/Subject_{Study-Wide} = \frac{\sum Applications_{Study-Wide}}{n_{all\ subjects}}$$

8b) $$Avg.Applications/Subject_{Cohort\ X} = \frac{\sum Applications_{Cohort\ X}}{n_{Cohort\ X}}$$

Equation 9. % ulcer size reduction

9a) $$\%\ ulcer\ size\ reduction = \frac{Ulcer\ size\ at\ last\ treatment\ visit - Ulcer\ size\ at\ randomization\ visit}{Ulcer\ size\ at\ randomization} * 100$$

11.1.3. Other Variables

Discontinuations

The difference between treatments, both overall and for each primary reason, will be compared by using a 2-sided Fisher's exact test.

Demographic and Baseline Characteristics

Comparisons between treatment groups of continuous variables will be made by using a one-way analysis of variance with treatment as a factor. For categorical variables, the Fisher's exact test will be used. All tests will be 2-sided and performed at the 0.05 level of significance.

Time-to-Event Data

Time-to-event endpoints including time-to-complete-wound-closure/healed will be evaluated using the Kaplan-Meier method. The log-rank test will be used to compare the distributions between two treatment groups.

Rate of Wound Closure, as Assessed by Computerized planimetry

Analysis of Covariance (ANCOVA) will be used to compare the rate of wound closure for the two treatment groups.

Safety Data

The primary safety endpoint for this study is any severe device-related complication where relationship to the device was assessed by the clinical event committee possible, probably, or definite. Fisher's exact test will be used to compare incidence rates of serious device-related complications as well as for any device-related complication, and for specific complications between the treatment group and the control group.

12. CHANGE FROM PLANNED ANALYSIS

Independent photograph review data analysis
The independent photograph review was done by three independent investigators, the data has been collected and evaluated. However, due to the flawed methodology of data assessment, the data is not going to be analyzed and will not be presented in CSR

Wound closure status at Week 4
Wound closure status at Week 4 is determined as the wound closure by investigator assessment, and is not be confirmed by the 2-week follow-up visit.

13. REFERENCES

1. T-AEPDFU-001 Protocol v 3.0 FINAL