Statistical Analysis Plan

for

CTP006-2

AVITA Medical Americas, LLC

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A Prospective Multicenter Randomized Controlled Clinical Study to Investigate the Safety and Effectiveness of RES® Regenerative Epidermal Suspension Prepared with the RECELL® Device Compared to Standard of Care Dressings for Treatment of Partial-thickness Burns in Infants, Children and Adolescents (Aged 1 – 16 Years)

CTP006-2

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DOCUMENT HISTORY

Revision Date	Author	Version	Reason for Change
05Mar2019	Elizabeth Kane	A	NA – Initial Version
15May2019	Elizabeth Kane	B	Added clarity around analysis populations to be used in interim and final analyses, added additional information regarding the FS score and added a sensitivity analysis for pain recovery endpoint.
07Feb2023	Patrick Walker	3.0	Updates to align with Rev 5 of the protocol.

1 ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ABA	American Burn Association
BOQ	Burn Outcome Questionnaire
BSA	Burn Surface Area
CEC	Clinical Events Committee
CI	Confidence Interval
CRF /eCRF	Case report form / electronic Case Report Form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
FDA	United States Food and Drug Administration
FLACC	Face, Legs, Activity, Cry, Consolability
FPS-R	Faces Pain Scale-Revised
F-S	Finkelstein-Schoenfeld (F-S)
IMM	Independent Medical Monitor
ITT	Intent-To-Treat Population
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-To-Treat Population
POSAS	Patient and Observer Scar Assessment Scale
PP	Per-Protocol Population
RES	Regenerative Epidermal Suspension
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
TBSA	Total body surface area
TEAE	Treatment emergent adverse event

2 SUMMARY

TITLE	A Prospective Multicenter Randomized Controlled Clinical Study to Investigate the Safety and Effectiveness of RES® (Regenerative Epidermal Suspension) Prepared with the RECELL® Device Compared to Standard of Care Dressings for Treatment of Partial-thickness Burns in Infants, Children and Adolescents (Aged 1–16 Years)
PREFACE	This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for AVITA Medical Americas, LLC protocol CTP006-2. This study is being completed to assess the safety and effectiveness of RECELL® for the treatment of partial-thickness burns in infants, children and adolescents (Aged 1–16 Years). The following documents were reviewed in preparation of this SAP: • Clinical Research Protocol CTP006-2, issued 11DEC2020 • Data Monitoring Committee (DMC) Charter, issued 23APR2021 • Case Report Forms (CRFs)
PURPOSE	The purpose of this SAP is to outline the planned analyses in support of the Clinical Study Report (CSR) for protocol CTP006-2. Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP will be clearly identified in the respective CSR.
STUDY OBJECTIVES	To demonstrate that RECELL treatment of partial-thickness burn injuries can safely and effectively increase the incidence of Day 10 healing compared with a standardized wound dressing. Also, the effects of both treatments on the incidence of conventional autografting, pain, itching, scarring, health-related quality of life and resource utilization will be investigated.
STUDY DESIGN	This is a prospective, parallel-arm, randomized (1:1), blinded evaluator, multicenter trial. Infants, children, and adolescents (aged from 1 through 16 years), male and female, with a burn injury that is no more than 30% of their total body surface area (TBSA) and no more than 10% TBSA is full-thickness burn injury, will be considered for participation. Randomization and assigned treatment must be performed within 72 hours of the burn injury for a subject to be treated within this study. Qualifying subjects will be randomized 1:1 either to treatment with RECELL or to Control (Mepilex® Ag Wound Dressing). Randomization will be stratified by investigational site and total burn area (<10% TBSA and ≥10% TBSA). If there is more than one partial-thickness burn wound, the largest partial-thickness burn wound meeting eligibility requirements will be identified as the Index Burn (the burn wound that will be compared for effectiveness outcomes). The Index Burn will be a contiguous area at least 160 cm^2 that excludes the face, hands, feet and genitalia.

	In order to evaluate the impact of study treatment on quality of life and health economic outcomes, unless clinical circumstances dictate otherwise, all of the subject's partial-thickness burn wounds, including any non-index burn(s), should be treated at the initial procedure according to the randomized treatment assignment. For subjects randomized to RECELL, skin sample harvesting and treatment should be performed in accordance with the RECELL Instructions for Use. Prior to application of RES, necrotic tissue is to be excised. The skin sample size required for processing is approximately 1/80th of the area to be treated. RES may be applied to the RECELL donor site at the investigator's discretion. For subjects randomized to Control, burn wounds should be cleaned per local standard practice prior to application of Mepilex® Ag Wound Dressing. Mepilex® Ag Wound Dressing will be applied in accordance with the manufacturer's Instructions for Use. Subjects should be seen for dressing changes as clinically indicated. Primary Effectiveness Assessments: Day 10 and Day 28 post-treatment, the Index Burn will be evaluated via direct visualization by a qualified local clinical investigator blinded to treatment allocation (Blinded Evaluator) to assess Index Burn healing, unless the Index Burn has been autografted. At all follow-up visits, the Index Burn will be photographically documented using standardized digital imaging. From these images, the percent re-epithelialization will be determined via photographic planimetry by a third-party centralized image vendor. A random selection of digital tracings will be reviewed by an Independent Medical Monitor to confirm the correct tracing of re-epithelialized areas reported by a third-party centralized image vendor. During the acute follow-up period, the investigator will determine whether autografting of the Index Burn is required. Autografting is typically indicated when there are no signs of improvement or healing, when the investigator expects no further wound healing in the next 7 to 11 days, or when a contiguous area greater than 0.5% TBSA is unhealed. Index Burns requiring conventional autografting will be evaluated as clinically indicated. Standardized digital images of Index Burns taken during acute follow-up, including images taken the day the investigator made a decision to autograft will be presented, out of time sequence, to an Independent Medical Monitor (blinded to treatment allocation and investigator's determination) to review.

	Longer-term follow-up visits will be performed at Weeks 8, 16, 24, 36 and 52 post-treatment (irrespective whether a subject had conventional autografting of the Index Burn). At the Week 16, 24, 36 and 52 post-treatment visits, scar outcomes and disease-specific quality of life will be assessed. Scar outcomes will be measured using the Patient and Observer Scar Assessment Scale (POSAS) questionnaire, which includes components for both the Blinded Evaluator and the subject (or parent/guardian, as appropriate). Patient- and family-reported quality of life outcomes will be captured via the age-specific Burn Outcomes Questionnaire (BOQ). The BOQ evaluates several domains specific to longer-term burn outcomes including physical function, appearance, satisfaction and emotional health among others. Investigator treatment preference will be documented for each treating investigator, at each burn center, following the investigator's last subject's last visit. During the longer-term follow-up visits, the preferred method is in-person clinical visits, however (if necessary), these follow-up visits may be conducted remotely (e.g., via telemedicine) with the exception of the Week 52 visit. Treatment-related adverse events (e.g., infection, wound breakdown, etc.) are to be recorded for the Index and Non-Index Burn wounds as well as for donor sites.
ENDPOINTS	Primary: The study's **primary effectiveness endpoint** is incidence of Index Burns with Day 10 healing post-treatment, evaluated by an observe blinded to treatment allocation, with confirmation at Day 28. If the Index Burn undergoes a secondary surgical treatment for closure (including conventional autografting) prior to the Day 28 visit, this will be considered an endpoint failure. The hypothesis to be evaluated is whether the incidence rate of Day 10 healing post-treatment is greater (superior) with RECELL treatment vs. Control treatment. The study's **safety endpoint** is incidence of treatment-related adverse events and all serious device-related adverse events. Secondary: Specific secondary endpoints to be investigated for potential labeling claims include the following: 1. Incidence of Index Burn Day 21 post-treatment healing (confirmed on Day 28). 2. Percent area of Index Burn requiring autografting. 3. Incidence of conventional autografting to achieve Index Burn healing. Each endpoint will be tested in a fixed hierarchical method at a one-sided 0.025 significance level in the above order. These secondary

	endpoints/hypotheses will only be evaluated if the null hypothesis for the primary endpoint is rejected in the appropriate direction, and each secondary endpoint will only be evaluated if the null hypothesis of equality, for the endpoint preceding it in the list above, is rejected in the appropriate direction. **Tertiary:** 1. Absolute area (cm^2) of Index Burn requiring autografting. 2. Index Burn pain scores at dressing changes assessed by the health care provider performing the dressing change using the Face, Legs, Activity, Cry, Consolability (FLACC) Scale. 3. Subject reported Index Burn pain scores at dressing changes. 4. Percent epithelialization of the Index Burn per digital planimetry. 5. Index Burn POSAS scar ratings. 6. BOQ Outcomes (raw scores and recovery curves for all domains), with baseline at Day 10. 7. Investigator treatment preference. 8. Health economics/medical resource utilization (determined using CRF data in conjunction with UB-04 and/or similar hospital claim forms for billing purposes to collect costs associated with the initial hospital care and readmissions during follow-up as applicable). 9. Index Burn Itch Man Scale ratings.
INTERIM ANALYSES	An interim analysis will be conducted once approximately 50% of total enrollment has completed the primary effectiveness endpoint follow-up (i.e., 80 subjects have been randomized and reached the Day 28 healing confirmatory visit or would have reached the Day 28 visit had they not prematurely withdrawn). At that time, study enrollment may be discontinued due to futility or demonstration of effectiveness. If enrollment continues, a sample size re-estimation will be performed, and the sample size may be adjusted upwards to a maximum of 300 randomized subjects. Safety data will be reviewed and adjudicated by an Independent Medical Monitor. A Data Monitoring Committee (DMC) will be responsible for interim review of safety and effectiveness data and will be responsible for reviewing data from the interim and sample size re-estimation analyses. No other interim analyses are planned.
FINAL ANALYSES	All final planned analyses identified in this SAP will be completed after the last subject has completed 52 weeks follow-up.

3 Study Objectives and Endpoints

3.1 Study Objective

The primary objective of this study is to demonstrate that RECELL treatment of partial-thickness burn injuries can safely and effectively increase the incidence of Day 10 healing compared with a standardized wound dressing. Also, the effects of both treatments on the incidence of conventional autografting, pain,

itching, and scarring will be investigated for the Index Burn while health-related quality of life and resource utilization will be investigated for the patient as a whole.

3.1.1 PRIMARY EFFECTIVENESS ENDPOINT

The **primary effectiveness endpoint** is incidence of Index Burns with Day 10 healing post-treatment, evaluated by an observer blinded to treatment allocation, with confirmation at Day 28. If the Index Burn undergoes a secondary surgical treatment for closure (including conventional autografting) prior to the Day 28 visit, this will be considered an endpoint failure.

3.1.2 SECONDARY EFFECTIVENESS ENDPOINTS

Secondary endpoints to be investigated for potential labeling claims include the following:

1. Incidence of healing Index Burn Day 21 post-treatment healing (confirmed on Day 28). The hypothesis to be evaluated is that the incidence rate of Day 21 healing will be superior in the RECELL treatment group.

2. Percent area of Index Burn requiring autografting. The hypothesis being evaluated is that the percent area of the Index Burn requiring autografting will be less in the RECELL treatment group.

3. Incidence of conventional autografting to achieve Index Burn healing. The hypothesis being evaluated is that subjects in the RECELL group will less frequently require conventional autografting of the Index Burn area.

3.1.3 TERTIARY EFFECTIVENESS ENDPOINTS/ADDITIONAL DATA COLLECTION

Other endpoints/data collection include:

1. Absolute area (cm^2) of Index Burn requiring autografting.

2. Index Burn pain scores at dressing changes assessed by the health care provider performing the dressing change using the Face, Legs, Activity, Cry, Consolability (FLACC) scale.

3. Subject reported Index Burn pain scores at dressing changes.

4. Percent epithelialization of the Index Burn per digital planimetry.

5. Index Burn POSAS scar ratings.

6. BOQ Outcomes (raw scores and recovery curves for all domains), with baseline at Day 10.

7. Investigator treatment preference

8. Health economics/medical resource utilization (determined using CRF data in conjunction with UB-04 and/or similar hospital claim forms for billing purposes to collect costs associated with the initial hospital care and readmissions during follow-up as applicable).

9. Index Burn Itch Man Scale ratings.

3.1.4 SAFETY

Safety of the RECELL Device will be based on the evaluation of the incidence of treatment-related and serious device-related adverse events (AEs). AEs will be documented for both the Index and Non-Index Burn as well as donor sites. For all AEs, the investigator must provide an assessment of the event, treatment resolution, and relationship to the investigational device.

4 SAMPLE SIZE

Qualifying subjects will be randomized 1:1 either to treatment with RECELL or to Control (Mepilex® Ag Wound Dressing). Randomization will be stratified by investigational site and total burn area (< 10% TBSA vs. ≥ 10% TBSA). Randomization details are documented within the Randomization Plan.

Based on medical input, the estimated proportion of subjects with Day 10 healing is anticipated to be approximately 75% for the Control group. It is estimated that the proportion of RECELL subjects with confirmed day 10 healing will be 92.5%. Assuming power of 80%, using a one-sided z-test of proportions and one-sided alpha of 0.025 requires 69 subjects per group (138 subjects total). The total sample size has been increased by 12% to 160 subjects to adjust for missing data.

5 SEQUENCE OF PLANNED ANALYSES

5.1 INTERIM ANALYSES

5.1.1 INTERIM ANALYSES FOR DESIGN ADAPTATION

A formal unblinded interim analysis comparing treatments on the primary endpoint will be conducted once 50% of total enrollment has completed for the primary effectiveness endpoint follow-up (i.e., 80 subjects have been randomized and reached the Day 28 healing confirmatory visit or would have reached the Day 28 visit had they not prematurely withdrawn). An independent biostatistician who is unrelated to the day-to-day conduct of the study will conduct this unblinded interim analysis and report results to the Data Monitoring Committee (DMC).

The unblinded interim analysis will be based on O'Brien-Fleming stopping rules. At the interim look, the one-sided p-value will need to be less than or equal to 0.00153 with results favoring RECELL in order to stop the study for reasons of overwhelming effectiveness of RECELL; the one-sided p-value will need to exceed

0.45604 to stop the study for futility. The one-sided p-value at the final analysis needs to be less than or equal to 0.02496, rather than the usual 0.025 required for a study without an interim analysis. This interim analysis will be based on all randomized patients with imputation of missing data to be carried out as discussed at the end of this section.

If the criterion for early stopping is not met, a conditional power calculation and sample size re-estimation will be performed by an independent statistician and will be presented to the independent DMC. The sample size re-estimation analysis will be performed according to the Mehta & Pocock Promising Zone approach and the DMC may recommend adjusting the sample size upwards (to a maximum of 300 randomized subjects) as indicated by the sample size re-estimation analysis, as long as the conditional power for success by the protocol-specified final sample size is in the promising zone (38% - 80%).

Specifically, at the DMC meeting to review the interim effectiveness analysis, the following will take place:

- DMC will inspect the p-values calculated for stopping the trial for overwhelming effectiveness or futility and make a formal recommendation to continue or discontinue the trial as appropriate.
- If the criterion for early stopping is not met, DMC will inspect the conditional power for achieving a successful trial for the current protocol-specified sample size under the assumption that the observed interim treatment effect size is the true treatment effect size.
- If the conditional power for a beneficial RECELL effect under the protocol-specified sample size is between 38% and 80% (the promising zone), the DMC may recommend an increase of the sample size to maintain conditional power of 80%. As discussed in Mehta and Pocock (2011) such a sample size increase will not require a penalty to the final significance level. The maximum sample size increase will be to increase the randomized sample size of 160 subjects to 300 subjects.
- If the conditional power under the protocol-specified sample size is <38% or if it is greater than 80%, then the final sample size will remain as is specified in the protocol.

This analysis will be performed on the mITT population with imputation for missing data first being carried out using the multiple imputation method described in Section 8.3 below (the multiple imputed z-statistic will be used in the calculation of conditional power). The results of the sample size re-estimation, regardless of outcome, will be summarized and reported to the FDA.

In addition to the sample size re-estimation analysis, the report for the interim analysis will include additional output as outlined in the DMC charter.

5.1.2 REPORTS FOR DMC

Avania will provide regular data summaries to the DMC members for review: quarterly during enrollment and bi-annually thereafter. These documents will include a summary of adverse event data, by treatment group, both adjudicated (to the extent possible) and non-adjudicated as reported by the sites. Members

will review the report and provide acknowledgement and/or questions to the DMC Liaison. If a committee member sees a concerning trend, he/she will contact Avania to set up a DMC conference call. Avania will be responsible for scheduling this call.

These safety update summaries may include the following:

- Subject Accountability
- Site Enrollment
- Demographics
- All SAEs
- All Treatment-Related Adverse Events (by location and seriousness: Donor Site, Index Burn Site, Non-Index Burn Site, Non Burn Site; Serious/Non-Serious)
- Serious Device Related Adverse Events (by location: Donor Site, Index Burn Site, Non-Index Burn Site, Non Burn Site)
- Wound Healing Durability
- Specific Treatment Related AEs
    - Incidence of Infection (Mild, Moderate, Severe)
    - Allergic Response to Trypsin
    - Scars requiring subsequent surgical intervention
- Procedure/Device Observations resulting in adverse event
- Any Unexpected or Unanticipated Adverse Device Effects
- Major Protocol Deviations

Modifications and/or additional tables/listings may be produced and distributed to the DMC per request of the committee, Avania, or Sponsor.

5.2 Final Analyses and Reporting

All final, planned, analyses identified in the protocol and in this SAP will be performed only after the last subject has completed 52 weeks follow-up. Key statistics and study results will be made available to AVITA Medical Americas following database lock. Any post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported as necessary. Any results from these unplanned analyses will also be clearly identified as post-hoc analyses.

6 Analysis Populations

6.1 Intent to Treat Population (ITT)

The ITT population will consist of all enrolled subjects who are randomized with data analyzed according to randomized treatment assignment. A sensitivity analysis for the primary and secondary effectiveness endpoints will be performed in the ITT population.

6.2 Modified Intent to Treat Population (mITT)

The mITT population will consist of all enrolled subjects who are randomized and treated, with data analyzed according to randomized treatment assignment. This population will be utilized as a primary analysis population for the primary and secondary effectiveness endpoints.

6.3 Per-Protocol Population (PP)

The PP population will consist of mITT subjects who do not have major protocol deviations with data analyzed according to treatment received. This population will be utilized as a secondary analysis population for the primary and secondary effectiveness endpoints. Major protocol deviations are described in section 7.4.

6.4 Safety Population

The safety analysis population includes all randomized, treated subjects. This is the primary analysis set for safety. Subjects will be analyzed for safety based on the treatment received.

7 General Issues for Statistical Analysis

Data collected in this study will be reported using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation [SD], minimum, and maximum). Categorical variables will be summarized using frequencies and percentages of subjects in each category. All results will be presented by treatment and appropriate subject populations. All statistical tests will be performed as a one-sided 0.025 level of significance unless otherwise specified below.

Data listings will be presented sorted by subject number and treatment. All data will be included in the data listings.

Analysis data sets, statistical analyses and associated output generated by Avania will be generated using SAS® Software version 9.4 or later.

7.1 Disposition of Subjects and Withdrawals

The number and percent of subjects in each analysis population will be presented both overall and by treatment group, with percentages based on the ITT population. This will be presented overall and by investigative site.

All treated subjects will be followed for a minimum of 52 weeks (± 28 days) post-treatment. Acceptable reasons for not evaluating a subject through the 52-week follow-up period include:

a) Subject Lost to Follow-Up: Unable to locate subject despite documented attempts to notify the subject via three telephone calls and one registered letter. A subject will not be considered lost to follow up until the time of the last scheduled follow-up visit.

b) Subject (or Parent/Legal Guardian) Request to Withdraw: The subject (or parent/guardian) requests to terminate his/her involvement in the study. To the extent possible an exit interview should be conducted with the subject to assess the subject's specific reason(s) for study withdrawal. The treatment area healing status at the time of withdrawal is to be documented.

c) Subject Death: Every attempt should be made to document the cause of death. An autopsy report should be obtained if available.

All subjects who provide informed consent will be accounted for. The frequency and percent of subjects who completed each scheduled assessment will be presented in a table overall and by treatment group.

The number and percentage of ITT patients prematurely withdrawing will be presented overall and by reason of discontinuation within each treatment group for the study and by investigative site.

7.2 Methods for Withdrawals and Missing Data

All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. Since effectiveness endpoints are assessed acutely 10- and 28-days following randomization, it is anticipated that there will be minimal missing data. In the case of missing data for a scheduled visit, if there is an unscheduled visit within the respective scheduled visit range, the data from the unscheduled visit will be used for analysis. Note: Data from an unscheduled visit will not replace data that is provided for the scheduled visit.

The primary effectiveness endpoint analysis will be on the mITT population, with secondary analysis on the PP population. In the mITT population, subjects may have missing information on healing, primarily due to premature withdrawal from the study. The analyses performed on the mITT population with available data will be considered primary. However, as sensitivity analyses, the primary endpoint analysis will be repeated on the entire mITT population, where missing data for the components of the primary endpoint will be imputed as outlined directly below; there will be no imputation for other endpoints in the study.

Subjects who are missing healing status will be considered as "missing data subjects". Missing healing status will be imputed using a logistic regression multiple imputation approach for dichotomous outcome data. In this approach, missing healing status will be imputed from logistic regression models with independent variables of age, gender, and other covariates including: randomized treatment group, anatomical location of burn, % TBSA, % BSA of Index Burn, % BSA of full-thickness burns, race, ethnicity, Fitzpatrick skin type, diabetes, smoking, nutritional status, time from initial injury to initiation of study treatment in days, time from initial injury to presentation for definitive burn care in days, and inclusion of joint within Index Burn. This will be performed 50 times in order to generate 50 "complete" datasets. The one-sided z-test of proportions assessing treatment difference will be carried out on each of the 50 complete datasets, with the results being combined across the 50 complete datasets using standard multiple imputation theory to obtain one overall one-sided p-value comparing the two treatments on the primary endpoint after accounting for missing data.

7.3 Protocol Violations

The following are considered major protocol deviations and will exclude a subject from the PP population:

- No endpoint data
- Conventional autografting prior to 10 days post burn
- Inclusionary/exclusionary deviations
- Missing Index Burn healing closure confirmation
- Other significant protocol non-compliance that may confound evaluation of healing (e.g., use of prohibited medications/treatments, inappropriate primary dressing, etc.). Subjects with such non-compliance will be determined prior to database lock and unblinding.

The number and percentage of subjects with each protocol deviation will be presented by treatment group and overall for the Safety Population.

7.4 Multiple Comparisons and Multiplicity

The three secondary endpoints listed in Section 3.1.2 will be tested one at a time in a fixed hierarchical method in the order given in Section 3.1.2. The first endpoint will be compared between treatments at a one-sided 0.025 level of significance. If the null hypothesis is rejected, then RECELL will be considered statistically superior to control on incidence of healing at Day 21 and treatment comparison analysis will proceed to the 2nd secondary hypothesis. This process will continue to the 3rd secondary hypothesis as long as the prior hypothesis is rejected at a one-sided 0.025 level of significance. These secondary endpoints/hypotheses will only be evaluated if the null hypothesis for the primary endpoint is rejected.

7.5 Assessment of Homogeneity

A poolability analysis will be performed to assess homogeneity of treatment difference on the primary endpoint across investigative sites. If there are less than 8 subjects in the population from an investigative site, the data from that site will be pooled with data from other investigative sites closest to it geographically. Pooling will be determined before the treatment blind is broken and prior to inspecting the outcome data.

The following will be carried out on the mITT and PP populations (available data): Assessment of homogeneity of treatment difference on the primary endpoint will be carried out using logistic regression with treatment, investigative site, and treatment-by-investigative site interaction as the independent variables. Of interest is the significance of the treatment-by-investigative site interaction.

If the treatment-by-investigative site interaction effect is significant at a 0.10 level of significance, then analyses within investigative site will be further inspected. If the interaction is not significant or if it is significant but the direction of the effect is the same in all investigative sites, then investigative sites will be

pooled for the final analysis. Otherwise, demographics within site will be inspected to assess if differences in site demographics may be causing the interaction.

There will be no imputation of missing primary outcome data for the poolability analysis.

7.6 Timing of Assessments and Events for Analysis

Study days will be calculated relative to the date of initial study treatment (i.e., Day 1 is the date of receipt of study treatment). Day 10 and Day 28 are based on days post study treatment and correspond to overall study days 11 and 29.

8 Demographics and Other Baseline Characteristics

The analyses described below will be carried out for the mITT population.

8.1 Demographics

Demographic and baseline characteristics, including age, sex (and if female, pre-pubescent or post-pubescent/menstruating), race, and ethnicity will be summarized by descriptive statistics by treatment group including the mean, median, standard deviation, quartiles, minimum, and maximum for continuous variables and number and percent of patients in each category for categorical variables. Percentages are based on the number of subjects in the mITT analysis population except for pubescent status where percentages are based on the number of females in the mITT analysis population.

8.2 Concurrent Medications and Procedures

Concomitant medications will be summarized in a table as number and percentage of patients taking at least one concomitant medication. The number and percentage of patients taking at least one concomitant medication pertaining to pain, pertaining to itching, and pertaining to wound healing (i.e. antibiotics, steroids, topical wound treatments, etc.) will be presented. Similar analyses will be repeated for concomitant procedures and/or therapies. Details for concomitant medications/procedures will be listed by subject.

8.3 Baseline Medical History

The number and percentage of mITT patients in each ASA physical classification score (I – VI) will be presented for each treatment group.

The number and percentage of mITT subjects with each recorded risk of impaired wound healing (none, current smoker, inadequate nutrition/malnutrition, immunodeficiency, obesity, diabetes, other) will be presented for each treatment group.

Relevant and other past/current medical history will be summarized by treatment group in a table. Conditions include eczema, heart murmur, asthma or reactive airway disease, bronchitis/ pneumonia, recurrent ear/sinus infections, fractures, diarrhea/ constipation, head injuries, seizures,

headache/migraines, mentally challenged or learning disabilities/ ADD/ ADHD, depression/ anxiety, substance abuse, vision problems, hearing problems, environmental allergies, food allergies, urinary tract infections, thyroid disease, diabetes, anemia, cancer, genetic syndromes and others. The summary will include the subject counts and percentages of mITT patients with a medical history for each body system within each treatment group.

8.4 Baseline Physical Exam

Baseline weight, height, vital signs and Fitzpatrick skin type will be summarized in a table for the mITT analysis population by treatment group. The summary will include the mean, standard deviation, N, median, quartiles, minimum, and maximum of height, weight, temperature, systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate. Fitzpatrick skin type will be summarized with subject counts and percentages.

The number and percentage of mITT subjects with an abnormality for each body system (head/neck, eyes, ENT, lymphatic, cardiac, respiratory, abdomen/GI, neurological, extremities, spinal, musculoskeletal, other) at baseline will be presented by treatment group.

8.5 Index Burn Injury Assessment

Characteristics of the burn injury will be summarized in a table by treatment group. Etiology, prior treatment (yes/no), and %TBSA (<10% vs ≥10%) will all be summarized with subject counts and percentages. Duration of injury to treatment (calculated) and % TBSA will be summarized using mean, standard deviation, N, median, quartiles, minimum and maximum.

8.6 Surgical Procedure Characteristics

Data concerning the index burn donor site will be documented on the eCRFs. Location, size (cm^2 and % TBSA), surgical tool used, depth setting, RES application details (e.g., volume and details for application) and use of Tumescence will be summarized using appropriate descriptive statistics by treatment group for the mITT population.

Location and treatment (same/different from index burn) of non-index burns will be summarized. Conventional autografting for non-index full thickness burns will also be summarized.

For the index burn, location, method of debridement, and time to perform wound bed preparation will be summarized with subject counts and percentages. RECELL device and RES preparation information including number of RECELL devices used, area of donor skin used to create suspension, total prepared suspension volume and time to perform procedure will be summarized for subjects in the treatment group.

For subjects undergoing conventional autografting, the amount of surface area autografted (expressed as a percent of the original burn area) will be compared between treatment groups using a two-sided two-sample t-test for the mITT population.

9 EFFECTIVENESS ANALYSES

9.1 PRIMARY EFFECTIVENESS VARIABLE

The primary effectiveness outcome is incidence of Index Burns with Day 10 healing evaluated by an observer blinded to treatment allocation, with confirmation at Day 28. If the Index Burn undergoes a secondary surgical treatment (including conventional autografting) prior to the Day 28 visit, this will be considered an endpoint failure.

The hypothesis to be evaluated is whether the incidence of Day 10 healing post-treatment (confirmed at Day 28 post-treatment) is greater (superior) with RECELL treatment vs. Control treatment. The null and alternative hypotheses to be tested at a one-sided 0.02496 level of significance are:

$$H_0: P_R \leq P_C \text{ vs. } H_1: P_R > P_C$$

where P_R and P_C are the primary endpoint rates for RECELL and control, respectively. The null hypothesis will be tested using a one-sided z-test of proportions at a one-sided 0.02496 level of significance. Additionally, two-sided 95.008% confidence intervals will be presented for the difference between treatments.

9.2 SECONDARY EFFECTIVENESS VARIABLES

Specific secondary endpoints to be investigated for potential labeling claims include the following:

1. Incidence of Index Burn Day 21 healing (confirmed on Day 28). This variable will be tested in the same manner as the primary effectiveness variable as described in Section 10.1.

   The hypothesis to be evaluated is whether the incidence rate healing on or before Day 21 is greater (superior) with RECELL treatment vs. Control treatment. The null and alternative hypotheses to be tested at a one-sided 0.025 level of significance are:

   $$H_0: P_R \leq P_C \text{ vs. } H_1: P_R > P_C$$

   where P_R and P_C are the primary endpoint rates for RECELL and control, respectively. The null hypothesis will be tested using a one-sided z-test of proportions at a one-sided 0.025 level of significance. Additionally, two-sided 95% confidence intervals will be presented for the difference between treatments.

2. Percent area of Index Burn requiring autografting. The hypothesis being evaluated is that the percent area of the Index Burn requiring autografting will be less in the RECELL treatment group. The null and alternative hypotheses of interest are:

   $$H_0: \mu_R \geq \mu_C \text{ vs. } H_0: \mu_R < \mu_C$$

where μ_R and μ_C are the mean percent area of the Index Burn requiring autografting for RECELL and control, respectively. The null hypothesis will be tested using a Wilcoxon Rank Sum test at a one-sided 0.025 level of significance, due to the anticipated skewness of the data resulting from most patients not requiring autografting.

3. Incidence of conventional autografting to achieve Index Burn healing: The null and alternative hypotheses to be tested at a one-sided 0.025 level of significance are:

$$H_0: AG_R \geq AG_C \text{ vs. } H_1: AG_R < AG_C$$

where AG_R and AG_C are the autograft rates for RECELL and control, respectively. The null hypothesis will be tested using the one-sided z-test for proportions at a one-sided 0.025 level of significance. The two-sided 95% CI for the difference between treatment groups will be presented. Time between study treatment and autograft date will also be summarized using descriptive statistics and presented by subject in listings.

The three endpoints listed above will be tested one at a time in a fixed hierarchical method in the order given above. The first endpoint will be compared between treatments at a one-sided 0.025 level of significance. If the null hypothesis is rejected, then RECELL will be considered statistically superior to control on incidence of healing at Day 21 and treatment comparison analysis will proceed to the 2nd secondary hypothesis. This process will continue to the 3rd secondary hypothesis as long as the prior hypothesis is rejected at a one-sided 0.025 level of significance. These secondary endpoints/hypotheses will only be evaluated if the null hypothesis for the primary endpoint is rejected.

Analyses will be carried out for the mITT (primary) and PP (secondary) populations. There will be no imputation of missing data for these secondary endpoints.

9.2.1 Tertiary Effectiveness Variables

The following endpoints will be collected and analyzed for exploratory purposes (not for labeling):

1. Absolute area (cm^2) of Index Burn requiring autografting
2. Index Burn Pain scores at dressing changes assessed by the health care provider performing the dressing change using the Faces, Legs, Activity, Cry, Consolability (FLACC) scale.
3. Subject reported Index Burn pain scores at dressing changes.
4. Percent epithelialization of the Index burn per digital planimetry.
5. Index Burn POSAS Scar Ratings
6. BOQ Outcomes (raw scores and recovery curves for all domains), with baseline at Day 10.
7. Investigator treatment preference
8. Health economics/medical resource utilization
9. Index Burn Itch Man Scale ratings.

The percent epithelialization of the Index burn per digital planimetry will be compared between treatments using a Cochran-Armitage test for trend.

For autografted Index Burns, the total area requiring autografting will be compared between treatments using an independent two-sample t test.

Mean Index Burn pain scores at dressing changes as assessed by the health care provider and by the subject will be compared between treatments over time. For the analysis, subjects will contribute pain scores collected from time of treatment through healing; i.e., subjects will contribute multiple observations per subject. Treatment groups will be compared on average pain scores over time using a generalized estimating equation (GEE) analysis of variance. The study day in which the pain score was assessed will be included in the model as a continuous covariate. The within-subject correlation matrix on pain scores will be assumed to be unstructured; if there are issues with convergence, then it will be assumed to be exchangeable. Mean POSAS, BOQ and Itch Man Scale rating outcomes will also be compared between treatment in a similar manner.

All statistical tests comparing treatments will use a one-sided 0.025 level of significance (there will be no adjustment for multiple comparisons due to the tertiary nature of the analysis). There will be no imputation of missing data. These tertiary analyses will be carried out on the mITT and PP populations.

For health economics, the number and cost of resources (e.g. procedures, etc.) will be summarized by treatment group for the primary admission, and for any hospital readmissions if relevant. Additional details for analysis of health economics will be addressed in the Health Economics Statistical Analysis Plan.

10 Safety Analyses

Safety data will be analyzed using all observed data from the safety population.

Vital signs are collected throughout the study. A tabulation of descriptive statistics at each visit and for the change from baseline to each visit will be prepared for the following vital signs within each treatment group: height, weight, body temperature, systolic blood pressure, diastolic blood pressure, pulse rate, and respiratory rate.

11 Adverse Events

All adverse events (AEs) will be coded using the standardized Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, version 18.0 or greater.

11.1 Adverse Events

All treatment-related and serious adverse events occurring during the course of the clinical study whether related to the investigational device or otherwise, will be recorded on the AE eCRF. Collection of adverse events will commence post-randomization. Serious adverse events (SAEs) will be followed until resolved or until they have stabilized in the event of study closure. Non-serious AEs will be followed until the subject

completes the study. For all AEs, the investigator must provide an assessment of the event, treatment resolution, and relationship to the investigational device.

A treatment emergent adverse event (TEAE) is an event that began or worsened in severity after the randomized treatment is started. For each treatment group, the number and percentage of subjects with at least one TEAE will be presented by MedDRA system organ class (SOC) and preferred term (PT). The number and percentage of patients with serious TEAEs will be presented in a similar manner. These analyses will be repeated for TEAEs related to each of infection, allergic reaction, and scars requiring surgical intervention. These analyses will be repeated for treatment site and donor site specific serious TEAEs and for treatment site and donor site specific TEAES leading to premature discontinuation from the study. For each analysis, the treatment groups will be compared using Fisher's Exact test. The difference in rates and the two-sided 95% CI for the difference will be presented.

For TEAEs which cannot be attributed to the treatment site or donor site (e.g., headache), the number and percentage of patients with TEAEs, serious TEAEs, and TEAEs leading to premature discontinuation from the study will be presented by MedDRA SOC and PT.

Because a subject may experience more than one AE, summaries will provide both the number of subjects experiencing at least one event and the number of events within a reporting period. Percentages provided will be the percent of subjects experiencing one or more adverse events.

In addition, incidence of TEAEs will be presented by severity (mild, moderate, severe) and by relationship (at least possibly investigational device related, at least possibly study therapy related, at least possibly procedure related). Subjects experiencing an event within a given PT and SOC more than once will be counted under the maximum severity/relationship experienced.

A listing of all adverse events will include the subject number, AE number, days since index procedure, the AE SOC and PT, the severity of AE, whether or not the AE is classified as serious (SAE), the relationship of the AE to the investigational device or procedure, the action taken, the outcome, and the adjudication status.

11.2 Deaths

Should any subjects die during the course of the clinical trial, relevant information will be supplied in a data listing.

12 Other Planned Analyses

12.1 Planned Subgroup Analyses

The analyses comparing treatments on the primary endpoint will be carried out within the following subgroups for the mITT (imputed and available data) and PP populations: anatomical location of burn, %

TBSA (below median vs. above median), % BSA of study burn area (below median vs. above median), age (by subgroups; i.e., infants: age 1 to <2 years; children: (≥ 2 years to < 12 years) and adolescent: ≥ 12 years to ≤ 16 years, gender, race, ethnicity, Fitzpatrick skin type, diabetes, smoking, nutritional status, time from initial injury to initiation of study treatment in days (below median vs. above median), time from initial injury to presentation for definitive burn care in days (below median vs. above median), requirement for conventional autografting (yes/no). The purpose of within-subgroup analyses is not to show significant treatment difference within a subgroup, but to assess homogeneity of treatment difference across subgroups. Homogeneity across groupings will be assessed in a similar manner as the assessment of homogeneity across investigative site discussed above.

12.2 ITT Population

As a supportive analysis, the analysis of the primary and secondary endpoints will be repeated using the ITT population with available data.

12.3 Analysis of Additional Study Assessments

12.3.1 Index Burn Healing Assessment by Investigator

The investigator's healing assessment will be summarized by study visit and treatment group. The number and percentage of subjects in each category will be presented.

12.3.2 Time to Discharge

The time to discharge will be summarized descriptively by treatment group.

12.3.3 Index Burn Dressing Regimen

The dressing regimen for the index burn will be summarized descriptively by treatment group. Type of dressing, quantity of dressings, size of dressings, and number of dressing changes will be summarized for primary and secondary dressings. The number and percentage of subjects requiring additional dressings and of subjects encountering problems during dressing change will be summarized.

13 Reporting Conventions

All reporting will meet the standards of SOP-AS-GLOB-003 Data Analysis Reporting and SOP-AS-GLOB-006 Programming Standards.