STATISTICAL ANALYSIS PLAN

CONTINUED ACCESS PROTOCOL: Demonstration of the Safety and Effectiveness of ReCell combined with Meshed Skin Graft for Reduction of Donor Area in the Treatment of Acute Burn Injuries

Protocol # CTP001-7

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Study Number: CTP001-7

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Table of Contents

List of Tables

Table Number	Table Title	Analysis Population	(U)nique/ (R)epeat
14.1 Demographic Data			
14.1.1.1	Subject Enrollment and Disposition	All Populations	U
14.1.1.2	Subject Enrollment and Disposition by Site	All Populations	R
14.1.2	Subject Disposition by Visit	ITT Population	U
14.1.3	Number and Percentage of Subjects with Protocol Deviations	ITT Population	U
14.1.4	Demographic and Baseline Characteristics	Intent-to-Treat Population	R
14.1.5	Medical History	Intent-to-Treat Population	R
14.1.6	Physical Examination	Intent-to-Treat Population	R
14.1.7	Injury Assessment	Intent-to-Treat Population	R
14.1.8	Size and Location of Treated Areas and Donor Site for Initial Treatment	Safety Population	U
14.1.9	ReCell Treatment Information	Safety Population	U
14.2 Clinical Performance Data			
14.2.1.1	Co-Primary Effectiveness Endpoint: Confirmed Treatment Area Closure at (or prior to) Week 8	Per Protocol Population	U
14.2.1.2	Co-Primary Effectiveness Endpoint: Confirmed Treatment Area Closure at (or prior to) Week 8	Intent-to-Treat Population	R
14.2.1.3	Co-Primary Effectiveness Endpoint: Confirmed Treatment Area Closure at (or prior to) Week 8 by Gender	Per Protocol Population	U
14.2.1.4	Co-Primary Effectiveness Endpoint: Confirmed Treatment Area Closure at (or prior to) Week 8 by Site	Per Protocol Population	U
14.2.2.1	Co-Primary Effectiveness Endpoint: Expansion Ratio for ReCell versus Control Treatment	Intent-to-Treat Population	U
14.2.2.2	Co-Primary Effectiveness Endpoint: Expansion Ratio for ReCell versus Control Treatment	Per Protocol Population	R
14.2.2.3	Co-Primary Effectiveness Endpoint: Expansion Ratio for ReCell versus Control Treatment by Gender	Intent-to-Treat Population	U
14.2.2.4	Co-Primary Effectiveness Endpoint: Expansion Ratio for ReCell versus Control Treatment by Site	Intent-to-Treat Population	U

Table Number	Table Title	Analysis Population	(U)nique/ (R)epeat
14.2.3.1	Subject Treatment Preference at Week 24	Intent-to-Treat Population	U
14.2.3.2	Subject Treatment Preference at Week 24	Per Protocol Population	R
14.2.4.1	Patient and Observer Scar Assessment Scale – Observer Overall Opinion Score at Week 24	Intent-to-Treat Population	U
14.2.4.2	Patient and Observer Scar Assessment Scale – Observer Overall Opinion Score at Week 24	Per Protocol Population	R
14.2.5.1	Patient and Observer Scar Assessment Scale – Patient Overall Opinion Score at Week 24	Intent-to-Treat Population	U
14.2.5.2	Patient and Observer Scar Assessment Scale – Patient Overall Opinion Score at Week 24	Per Protocol Population	R
14.2.6.1	Treatment Area Closure by Study Visit by Blinded Evaluator	Intent-to-Treat Population	U
14.2.6.2	Treatment Area Closure by Study Visit by Blinded Evaluator	Per Protocol Population	R
14.2.7.1	Treatment Area Closure by Study Visit by Non-Blinded Evaluator	Intent-to-Treat Population	U
14.2.7.2	Treatment Area Closure by Study Visit by Non-Blinded Evaluator	Per Protocol Population	R
14.2.8.1	Patient and Observer Scar Assessment Scale by Study Visit – Observer	Intent-to-Treat Population	U
14.2.8.2	Patient and Observer Scar Assessment Scale by Study Visit - Observer	Per Protocol Population	R
14.2.9.1	Patient and Observer Scar Assessment Scale by Study Visit – Patient	Intent-to-Treat Population	U
14.2.9.2	Patient and Observer Scar Assessment Scale by Study Visit - Patient	Per Protocol Population	R
14.2.10.1	Blinding Effectiveness at Week 8 for Blinded Evaluator and at Week 24 for Subject	Intent-to-Treat Population	U
14.2.10.2	Blinding Effectiveness at Week 8 for Blinded Evaluator and at Week 24 for Subject	Per Protocol Population	R
14.2.11.1	Subject Treatment Preference by Study Visit	Intent-to-Treat Population	U
14.2.11.2	Subject Treatment Preference by Study Visit	Per Protocol Population	R
14.2.12.1	Inter-Rater Reliability for Assessment of Wound Healing at Week 8 by Site	Intent-to-Treat Population	U
14.2.12.2	Inter-Rater Reliability for Assessment of Wound Healing at Week 8 by Site	Per Protocol Population	R
14.3 Safety Data			
14.3.1 Study Procedure and Adverse Events			

Table Number	Table Title	Analysis Population	(U)nique/ (R)epeat
14.3.1.2.1	Overall Summary of Adverse Events	Safety Population	U
14.3.1.2.2.1	Incidence of Adverse Events	Safety Population	U
14.3.1.2.2.2	Incidence of Adverse Events for ReCell and Control	Safety Population	U
14.3.1.2.3	Incidence of Adverse Events by Severity	Safety Population	U
14.3.1.2.4	Incidence of Adverse Events by Relationship to Device	Safety Population	U
14.3.1.2.5	Incidence of Treatment-Emergent Device-Related Adverse Events	Safety Population	R
14.3.2 Other Serious and Significant Adverse Events			
14.3.2	Number and Percentage of Subjects with Selected Safety Events	Safety Population	U
14.3.4 Other Safety Data			
14.3.4.1	Subject Assessment of Pain by Study Visit	Intent-to-Treat Population	U
14.3.4.2	Summary of Treatment Areas Requiring Retreatment	Safety Population	U

List of Listings

Number	Title
16.2.1 Discontinued Subjects	
16.2.1.1	Study Completion and Discontinuation Information
16.2.1.2	Study Visits
16.2.2 Protocol Deviations	
16.2.2.1	Inclusion and Exclusion Criteria Not Met
16.2.2.2	Protocol Deviations
16.2.3 Subjects Excluded from Efficacy and Safety Analyses	
16.2.3.1	Randomization
16.2.3.2	Subjects Excluded from The Analysis Populations
16.2.4 Demographic Data	
16.2.4.1	Demographics and Impaired Wound Healing Risks
16.2.4.2	Medical History
16.2.4.3	Physical Examination
16.2.4.4	Vital Signs
16.2.4.5	Concomitant Medications
16.2.4.6	Concomitant Procedures/Therapies
16.2.4.7	Size of Treated Areas and Donor Site Areas
16.2.4.8	Overall Injury Assessment
16.2.4.9.1	ReCell Treatment Information Part 1
16.2.4.9.2	ReCell Treatment Information Part 2
16.2.5 Study Procedure/Device Data	
16.2.5.1	Anatomical Location and Grafting Plan for Each Treated Area
16.2.5.2	Size of Re-Treatment Area and Donor Site Areas
16.2.5.3	Anatomical Location and Grafting Plan for Each Re-Treated Area
16.2.5.4.1	Re-Treatment ReCell Treatment Information – Part 1
16.2.5.4.2	Re-Treatment ReCell Treatment Information – Part 2
16.2.6 Individual Efficacy Response Data	
16.2.6.1	Co-Primary Effectiveness Endpoint
16.2.6.2	Blinded Assessment of Treatment Area Closure
16.2.6.3	Non-Blinded Assessment of Treatment Area Closure
16.2.6.4	Subject Treatment Preference
16.2.6.5.1	POSAS Observer Scale – Part 1

Number	Title
16.2.6.5.2	POSAS Observer Scale – Part 2
16.2.6.6.1	POSAS Patient Scale – Part 1
16.2.6.6.2	POSAS Patient Scale – Part 2
16.2.6.7	Evaluator Blinding Effectiveness at Week 8
16.2.6.8	Subject Blinding Effectiveness at Week 24
16.2.6.9	Dressing Changed Compliance Weeks 1 – 10
16.2.6.10	Initial Primary and Secondary Wound Dressings
16.2.7 Adverse Event Listings	
16.2.7.1	Adverse Events
16.2.7.2	Device-Related Adverse Events
16.2.7.3	Serious Adverse Events
16.2.7.4	Adverse Events Specific to Study Treatment Areas
16.2.7.5	Selected Safety Events
16.2.7.6	Treatment Area Infection
16.2.8 Listings of Other Safety Assessments	
16.2.8.1	Subject Pain Assessment
16.2.8.2	Photography Information
16.2.9 Other Listings	
16.2.9	Dressing Placement Log

List of Abbreviations

AE	Adverse Event
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case Report Form
CSR	Clinical Study Report
eCTD	Electronic Common Technical Document
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
POSAS	Patient and Observer Scar Assessment Scale
PP	Per Protocol
PT	Preferred Term
RES	ReCell Epithelial Suspension
SAE	Serious Adverse Event
SOC	System Organ Class
TBSA	Total Body Surface Area

1.0 INTRODUCTION

This document details the statistical analysis plan for the study entitled "CONTINUED ACCESS PROTOCOL: Demonstration of the Safety and Effectiveness of ReCell combined with Meshed Skin Graft for Reduction of Donor Area in the Treatment of Acute Burn Injuries". It describes the proposed effectiveness and safety analyses, including planned summary tables and by-subject data listings. It is based on the August 25, 2016 version of the protocol and associated Case Report Forms (CRF).

The ReCell device is a stand-alone, battery operated autologous cell harvesting device containing enzymatic and carrier solutions, sterile surgical instruments, and spray applicators that is intended to provide cellular coverage of a wound site to initiate repair. ReCell is designed to allow for regeneration of skin without cell culturing, using a minimal donor site (i.e., $4cm^2$ donor for $320cm^2$ coverage; 80:1 expansion). The new epithelium is comprised of the patient's own skin cells. The ReCell Autologous Cell Harvesting device is an autograft-sparing technology indicated for use at the patient's point-of care for preparation of an autologous epithelial cell suspension to be applied to a prepared wound bed. Under the supervision of a healthcare professional, the suspension is used to achieve epithelial regeneration for definitive closure of burn injuries, particularly in patients having limited availability of donor skin for autografting.

The primary clinical benefit of the ReCell device in burn care is healing (primary closure) with reduced burden on the patient for the harvesting of skin needed for grafting. Complications associated with donor sites can be debilitating and include pain, infection and delayed healing. Study protocol CTP001-7 is designed to show the clinical benefit of the ReCell device. Specifically, the primary objective of this investigation is to show the use of ReCell decreases the requirement for donor skin harvesting for autografts without compromising healing. The secondary objective is to show improvements in scar outcomes with use of ReCell. Safety will also be evaluated.

2.0 STUDY OBJECTIVES

The overall purpose of this study is to provide continued access to the ReCell device following completion of protocol CTP001-6, and to allow for collection of supplementary clinical outcome data for the ReCell device when used as an adjunct to meshed grafts in subjects with acute thermal burn injuries requiring skin grafting for closure of burn injuries. Co-primary effectiveness endpoints include comparisons of: (1) the incidence of confirmed complete closure of the treatment (ReCell) vs control (i.e., healing) prior to or at 8 weeks as assessed by a blinded evaluator, and (2) the actual (treatment area to donor area) expansion ratios for the treatment (ReCell) vs control. Safety will be evaluated in terms of long-term durability, scaring necessitating surgical intervention and other adverse events.

3.0 STUDY DESIGN

3.1 Overview

This is a prospective, randomized, multicenter, evaluator blinded, within-subject controlled study in which enrollment of up to 60 subjects is planned. Patients 5 years or older with a total body surface area (TBSA) thermal burn injury between 5% and 50% (inclusive) will be considered for participation in this study. Following burn excision and confirmation of eligibility, a grafting plan will be developed and documented in accordance with investigators' standard of care. Among the excised areas, two comparable contiguous or non-contiguous areas (i.e., similar in burn injury depth, graft plan and size) each at least 300 cm^2 in size will be identified and labeled as Area A and Area B. The wound areas will be randomly assigned to receive grafting consistent with the Investigator's pre-identified graft plan (control) or to receive ReCell Epithelial Suspension (RES) applied over a graft more widely meshed than identified in the pre-specified graft plan. For example, if the control graft plan called for a 2:1 meshed graft, the ReCell-assigned area will be receive 3:1 meshed graft over-sprayed with RES. The donor area for skin allocated to ReCell and control treatments will be measured and documented. The two treatment areas will be compared with respect to healing, the relative amount of donor skin harvesting required and scar outcomes.

Follow-up visits will be performed at 1, 2, 4, 6, 8, 10, 12, 24, 36 and 52 weeks post initial treatment. A schedule of study assessments is outlined in Table 1. Acute healing and pain outcomes will be evaluated in the early post-operative period (i.e., through 12 weeks). Pain, healing durability and scar outcomes will be evaluated in the longer-term follow-up visits (i.e., 24, 36 and 52-week visits). Treatment-related and serious adverse events will be captured throughout the duration of the study. Treatment-area closure will be evaluated via direct visualization by the treating investigator and by a qualified clinical investigator blinded to treatment allocation (i.e., Blinded Evaluator). The blinded assessment will serve as the primary healing assessment. At all visits, all subjects' study treatment areas will be documented photographically using standardized digital photography. 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 patient.

The study will be conducted at up to 18 investigational sites in the United States.

Table 1: Study Assessments

Table 1: Study Visits/Procedures											
		Follow-Up Visits (Weeks Post-Treatment)									
Assessments	**Treat-ment**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**24**	**36**	**52**
Visit Window Interval	NA	±1 day	±3 days	±3 days	±3 days	±5 days	±5 days	±5 days	±14 days	±14 days	±28 days
Size of Donor Site	X (including re-treatment)	-	-	-	-	-	-	-	-	-	-
Photography Treatment Area †Pre-excision, post-excision & post grafting	X†	X	X	X	X	X	X	X	X	X	X
Photography Donor Area (Post-harvest)	X	-	-	-	-	-	-	-	-	-	-
Clinical (non-blinded) Assessment of Treatment Area Closure	-	X	X	X	X	X	X	X	X	X	X
Blinded Assessment of Treatment Area Closure [a]Treatment Area Endpoint	-	-	-	X	X	X[a]	X	X	-	-	-
Investigator Blinding Effectiveness Assessment	-	-	-	-	-	X	-	-	-	-	-
Subject Blinding Effectiveness Assessment	-	-	-	-	-	-	-	-	X	-	-
Subject Assessment of Pain	-	X	X	X	X	X	X	-	-	-	-
POSAS	-	-	-	-	-	-	-	X	X	X	X
Subject Satisfaction	-	-	-	-	-	-	-	X	X	X	X
Dressing Changes/ Concomitant Medications and Therapies	X	X	X	X	X	X	X	X	X	X	X
Treatment-Related and Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X

3.2 Method of Assigning Wound Areas to Treatment

Allocation of treatments to the treatment areas will be done at random, using a pre-determined random assignment of treatments to the two defined wound regions (A and B). Wound regions will initially be labeled A and B by the physician, and then an envelope will be opened, which will indicate which treatment to assign to A and which to B.

3.3 Blinding

The study subject is not to be told which application area was treated with the ReCell.

Blinded assessment of healing status will be evaluated in person by a qualified individual blinded to treatment assignment (i.e., Blinded Evaluator) at the Week 4 through Week 12 visits. Blinded Evaluators will have a minimum of 2 years clinical experience in assessing and treating acute burn wounds. For the blinded assessment, healing of the 2 treatment areas will be assessed one at a time (per subject) via direct visualization by the Blinded Evaluator who will be blinded to the treatment assignments of the wound areas. Prior to the healing assessment, subjects must be draped such that all grafted areas, with the exception of the wound area to be evaluated, are hidden from view. At no time are the 2 treatments areas to be viewed simultaneously by the Blinded Evaluator.

Blinding effectiveness assessments for both the Blinded Investigator and Subject will be performed at 8 weeks and 24 weeks respectively. The timing of these assessments corresponds to the primary and secondary effectiveness endpoints, respectively.

3.4 Determination of Sample Size

It is anticipated that up to 60 subjects may be accrued in the period between the time the protocol is approved and receipt of Food and Drug Administration (FDA) marketing approval for the ReCell device.

3.5 Changes and clarifications to the Protocol-Specified Analyses

Planned changes and clarifications from the analyses specified in the protocol are listed below.

- For the effectiveness endpoint analyses, the methods described by Fleiss (Statistical Methods for Rates and Proportions (2nd ed.), John Wiley & Sons, New York, 1981, p. 117) will be applied.
- Statistical methods for secondary effectiveness endpoints have been modified to standardize with the pivotal CTP001-6 clinical study:
    - A chi-square test of goodness of fit will be performed for the evaluation of subject satisfaction at 24 weeks (assuming expected cell counts are the same for both ReCell and Control) rather than a one-sided binomial test as stated in the protocol.
    - The 24 week Observer and Patient Overall Opinion score will be assessed by a two-sided paired t-test with $\alpha = 0.05$ rather than a one-sided paired t-test with $\alpha = 0.025$ as stated in protocol.
- Initially, an Interim Analysis was planned to occur at the same time of the ReCell market application submission. The interim analysis was canceled as there were insufficient subjects enrolled in the trial at the time of the regulatory application and therefore an analysis at that time would not have been informative.

4.0 EFFECTIVENESS AND SAFETY ENDPOINTS

4.1 Co-Primary Effectiveness Endpoints

4.1.1 Confirmed Treatment Area Closure at (or prior to) the Week 8 Visit

Treatment area closure is defined as complete re-epithelialization without drainage, confirmed at 2 consecutive study visits at least 2 weeks apart (e.g., at Week 6 and Week 8, or if a visit is missed, e.g. Week 6 then Week 8 and Week 10 would be used) by direct observation by a local investigator blinded to treatment assignment (i.e., Blinded Evaluator).

Note that secondary surgical procedures are allowed and anticipated during the 8-week period following the initial surgical procedure for definitive closure.

4.1.2 Ratio of Actual Expansion Ratios

The actual expansion ratio, computed as the ratio of measured treated area to the measured donor site area, will be calculated for the ReCell and control treatments. The actual expansion ratio for the ReCell-treatment will be compared to the actual expansion for the control. The actual expansion ratios will be compared as a new ratio (a ratio of ratios), i.e. ReCell-treated area/ReCell-associated donor site area: Control area/Control-associated donor site area.

Treatment area and donor area will be based on measurements of the treatment and donor site wound bed at the time of the grafting procedure (obtained intra-operatively). Calculation of expansion ratio will include any donor skin required for re-treatments performed to achieve wound closure, if applicable.

4.2 Secondary Effectiveness Endpoints

The following secondary effectiveness endpoints will be investigated.

- Subject Satisfaction at 24 Weeks: Subject satisfaction will be measured by asking the subject to specify which treatment region they are more satisfied with (Area A or Area B).
- POSAS – 24 Week Observer Overall Opinion Score: The observer component of the POSAS questionnaire requires the Blinded Evaluator to provide an overall opinion of the treatment area compared to normal skin scored from 1 (normal skin) to 10 (worst imaginable scar).
- POSAS – 24 Week Patient Overall Opinion Score: The patient component of the POSAS questionnaire requires the subject to provide an overall opinion of the treatment area compared to normal skin scored from 1 (normal skin) to 10 (worst imaginable scar).

4.3 Safety Endpoints/Assessments

Safety of the ReCell device will be based on the following:

4.3.1 Delayed Healing

Treatment areas that do not heal within 8 weeks from the primary study procedure, based on the investigator's assessment, will be considered to have delayed healing.

4.3.2 Infection

The presence of infection will be evaluated at each postoperative visit. Infection will be evaluated in accordance with standard clinical measures such as visual examination of the treatment areas for purulence, erythema, pain, tenderness, warmth, induration, and cellulitis or more severe systemic symptoms of infection. Infection assessment will take place for both the ReCell-treated and the control areas to for comparisons to be drawn.

4.3.3 Allergic Response to Trypsin

The allergic response to trypsin will be evaluated preoperatively and at every postoperative visit.

4.3.4 Treatment Area Durability

Wound durability, in terms of the incidence of recurrent wound breakdown following initial complete closure, will be documented as an adverse event.

4.3.5 Scars Necessitating Surgical Intervention

Scars that, in the opinion of the investigator, necessitate surgical intervention will be documented as adverse events. This includes but is not necessarily limited to: dermabrasion and/or laser resurfacing, contracture release and scar excision and regrafting.

4.3.6 Pain

Treatment area pain will be assessed at the follow-up visits Weeks 1, 2, 4, 6, 8 and 10 using a numeric pain scale of 1-10, where 1 represents no pain and 10 represents yes, very much from the Subject Assessment of Pain. Prior to Week 12, pain assessments are from the Subject Assessment of Pain. Beginning at Week 12 through Week 52, pain assessments will be from a question in the POSAS questionnaire (‘Has the scar been painful the past few weeks’) with a numeric scale of 1- 10, where 1 represents no, not at all and 10 represents yes, very much.

4.3.7 Adverse Events and Serious Adverse Events

All treatment-related adverse events (AEs) and serious adverse events (SAEs) occurring during the course of the clinical study (beginning from the initiation of the grafting procedure), whether related to the investigational device or otherwise, will be recorded on the AE Case Report Form. Treatment-related AEs are defined as AEs related to the care of the subjects’ burn injuries, regardless of whether the event is specifically related to study area A or B. For all AEs, the Investigator must provide an assessment of the event, its treatment resolution, and relationship to the investigational device.

4.4 Additional Data Collection

4.4.1 Unblinded Healing Assessment

Subjects treated under this protocol will be followed for wound healing by the treating investigator(s), and the assessments will be documented in the CRF. Extent of wound healing will be captured using the following five categories: 100%, 80-90%, 50-79%, 1-49%, 0%.

4.4.2 Subject Satisfaction and POSAS at Weeks 12, 36 and 52

Subject Satisfaction and POSAS ratings at Weeks 12, 36 and 52 will be documented and reported for each item and for the sum of all items (excluding the overall assessment).

4.4.3 Blinding Effectiveness

Blinding effectiveness will be evaluated for both the Blinded Evaluator and the Subject.

- At Week 8, the Blinded Evaluator will be asked to indicate which treatment each area received. Potential responses are ReCell, Control or unsure.
- At Week 24, the Subjects will be asked to indicate which treatment each area received. Potential responses are ReCell, Control or unsure.

5.0 STATISTICAL CONSIDERATIONS

5.1 General Methodology

The statistical analysis of the data obtained from this study will be performed using SAS® Version 9.3 or higher. Data collected in this study will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics, (number of subjects, mean, median, standard deviation, minimum and maximum). Categorical variables will be summarized using frequencies and percentages. All results will be presented by treatment. For the co-primary effectiveness endpoint for confirmed treatment area closure, the test will be evaluated by a 95% two-sided confidence interval for the difference in the proportion of subjects with confirmed treatment closure on or before Week 8. For the co-primary effectiveness endpoint of relative reduction in donor site area, the test will be one-sided with a 2.5% significance level, all other statistical tests will be two-sided at the 5% significance level, unless otherwise noted. All analyses proposed here are for informational purposes only. Any post-hoc or unplanned analyses not identified in this statistical analysis plan will be clearly identified in the Clinical Study Report (CSR).

Data listings will be sorted by subject number. Where appropriate (e.g., adverse events), data listing will be sorted by subject number and treatment. All date fields will be presented in a format of ddmmmyyyy (i.e., 01Jan2017) in the listings. All data will be included in the data listings.

Study days will be calculated relative to the date of initial device use. Day 1 will be the first day the device was used in the study, and the day prior to Day 1 will be Day -1. There will be no Day 0.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0

5.2 Adjustments for Covariates

No adjustments for covariates are planned.

5.3 Handling of Dropouts and Missing Data

The primary analysis will be performed on observed data. Every attempt will be made to contact subjects who are non-compliant or lost to follow-up, and such attempts will be documented in the subject's study record. All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. For evaluation of the co-primary effectiveness endpoints, it is anticipated that there will be minimal missing data. However, multiple imputation and sensitivity analyses (e.g., pattern mixture models) will be performed if appropriate to account for missing data.

5.4 Interim Analyses

No Interim Analysis is planned.

5.5 Multicenter Study

The study will be conducted at up to 18 investigational sites in the United States. For the co-primary endpoints, descriptive statistics will be presented by site.

5.6 Multiple Comparisons / Multiplicity

No adjustments for multiple comparisons will be necessary. The data collected under this protocol will be considered supplementary to the primary CTP001-6 cohort. P values, when presented, will be for informational purposes only.

5.7 Examination of Subgroups

Co-primary effectiveness endpoints will be summarized descriptively by gender and by site as appropriate.

5.8 Additional Variables

It is expected that additional variables not described in the SAP may be derived and summarized, or listed. This statistical analysis plan will not be amended for additional variables that are not related to the primary or secondary effectiveness endpoints. Any additional derived variables will be identified and documented in the SAS programs that create analysis files and in the CSR.

6.0 ANALYSIS POPULATIONS

6.1 Intent-to-Treat Population

The Intent-to-Treat Population will include all subjects who are randomized. Data will be analyzed based on the treatment assigned to an area, regardless of the actual treatment of the area. The Intent-to-Treat (ITT) population will be the primary analysis population for evaluation

of the superiority hypothesis for the co-primary effectiveness endpoint of donor area harvest requirements.

6.2 Per Protocol Population

The Per Protocol Population will include ITT subjects who receive both study treatments and have no major protocol deviations. Data will be analyzed based on the planned treatment of an area. The Per Protocol (PP) population will be the primary analysis population for the test of non-inferiority for the co-primary effectiveness endpoint of confirmed treatment area closure at or before 8-weeks post-treatment. The reason for considering the analysis based on the PP Population is that for tests of non-inferiority, it is generally thought to be more conservative to use the PP Population rather than the ITT Population. Other effectiveness endpoints will also be analyzed based on the PP Population. For all other effectiveness endpoints, the analyses based on the PP Population will be considered secondary analyses.

The following will be considered major protocol deviations that will exclude a subject from the PP population:

- Major inclusionary/exclusionary deviations
- Missing primary wound healing endpoint visit
- Other significant protocol non-compliance that may confound evaluation of healing (e.g., use of prohibited medications/treatments, inappropriate primary dressing, etc.).
- Treatment of an area differs from the assigned treatment of the area

The determination of whether a deviation meets the definition of a major protocol deviation will be done in a blinded fashion by a Sponsor representative and will be performed without knowledge of outcomes for the subject/treatment area in question. Exclusions from the PP population will be identified and documented prior to database lock.

6.3 Safety Population

The safety analysis population will include all enrolled subjects who received treatment with ReCell. Data will be analyzed based on treatment received. A subject who receives control treatment but did not receive ReCell treatment will be excluded from the Safety Population.

7.0 STUDY SUBJECTS

7.1 Analysis Populations

The number and percent of subjects in the Safety, ITT and PP will be presented. The percentages will be based on the number of subjects in the ITT population. In addition, the number of subjects in each population will be summarized by site.

Subjects who are excluded from the safety or PP population will be presented in a data listing, along with reasons for exclusion.

7.2 Subject Disposition

The number and percentage of subjects in the ITT population who complete the study will be summarized, along with the number and percentage of subjects who do not complete the study for each discontinuation reason as specified on the CRFs. The percentages will be based on the number of subjects in the ITT population.

The following will be summarized by visit for the ITT population:

- Number of subjects due for the visit
- Number of subjects with the visit
- Number of subjects with missed the visit
- Number of subjects who discontinued
- Number of subjects who are Lost-to-Follow up.

Inclusion/exclusion data and subjects disposition information will be presented by subjects in data listings, separately.

7.3 Protocol Deviations

The number and percentage of subjects in the ITT population who have protocol deviations will be summarized.

Protocol deviations will be presented by subject in a data listing.

7.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the ITT population.

The following baseline and demographic characteristics will be summarized by descriptive statistics:

- Age at time of informed consent
- Gender
- Race

- Pre-treatment vital signs (height, weight, temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate)

- Risks for impaired wound healing (none, current smoker, inadequate nutrition, other)

For general medical history and physical examination, the number and percentage of subjects with each medical condition or abnormality listed on the CRF will be summarized.

For injury assessment, the following characteristics will be summarized by descriptive statistics for the safety, ITT and PP populations:

- Duration of injury,

- Primary mechanism of burn injury

- Total estimated burn injury size

- Total estimated area requiring grafting

- Use of prior treatments for the injury

Duration of injury will be calculated as (treatment date-the initial injury date) + 1 if the complete injury date is known. If only the month and year of injury date are known, the day of injury will be imputed as 15. If only the year of injury is known, the duration of injury will be calculated as the year of treatment minus the year of injury onset in days.

Continuous variables will be summarized using the number of subjects, mean, standard deviation, median, minimum and maximum; categorical variables will be summarized using counts and percentages of subjects in each category.

7.5 ReCell and Control Wound Area and Donor Site Characteristics

Anatomical location of ReCell and Control Areas will be summarized by treatment. Primary excision technique, meshing ratio used and graft anchoring method will be summarized for ReCell and Control areas. Comparability between treatments in these characteristics will be assessed descriptively for the Safety population.

The size of the ReCell Treatment and Control Areas as well as the respective sizes of the donor sites will be summarized by treatment. Comparability between treatment in wound areas and donor sites will be compared using a paired t test for the Safety population.

7.6 ReCell Treatment Information

The following data concerning area ReCell processing parameters will be summarized using descriptive statistics for the Safety population:

- Number of ReCell devices used
- Total area of donor skin used to create suspension
- Any device malfunction?

- If malfunction result in Adverse Event
- If malfunction results in non-treatment with ReCell

ReCell processing parameters will be listed by subject.

7.7 Concomitant Procedure/Therapy and Medications

All concomitant procedures/therapies and medications will be listed by subject.

7.8 Dresssing Changes

Dressing changes will be listed by subject.

8.0 EFFECTIVENESS ANALYSES

The analysis based on the PP Population will be considered the primary analysis for the co-primary effectiveness endpoint of confirmed treatment area closure. The analysis based on the ITT Population will be considered the primary analysis for the co-primary endpoint of the ratio of ratios of donor skin area harvested/graft area. Analyses based on the ITT Population will be considered the primary analyses for all other secondary endpoints. Analyses based on the PP Population will be performed on all other secondary endpoints if the ITT and PP Populations differ. The co-primary effectiveness endpoints will be summarized by gender and by site using descriptive statistics. Where indicated, nominal P values (unadjusted), will be presented for informational purposes only.

8.1 Co-Primary Effectiveness Endpoint Analyses

8.1.1 Confirmed Treatment Area Closure at 8 Weeks

The 97.5% one-sided confidence interval for the difference of the proportions between the ReCell and control treatment areas healed prior to or at the 8-week visit will be computed using the normal approximation taking correlation into account (Fleiss, J.L. *Statistical Methods for Rates and Proportions* (2^{nd} ed.), John Wiley & Sons, New York, 1981, p. 117).

8.1.2 Co-Primary Effectiveness Endpoint - Ratio of Ratios of Donor Skin Area Harvested/Graft Area

The ratio of the area of donor skin harvested (inclusive of any secondary treatments) to study graft area for the ReCell-treated and control wounds will be calculated. From these values a "ratio of ratios" will be calculated as follows:

- (ReCell treatment area/corresponding donor area) / (control treatment area/corresponding donor area)

Donor skin measurements will generally be based on measurements obtained intra-operatively at the time of the primary procedure but will also include any donor skin required for re-treatments performed to obtain wound closure if applicable. A one sample t-test with a one-sided significance level of 0.025 will be performed.

Each ratio of ratios will be log-transformed using the natural logarithm (base e) before analysis. The point estimates of the geometric mean ratio will be calculated for the log-transformed ratio

of ratios and the corresponding 2-sided 95% CI will be calculated for the difference between log-transformed ratios, then exponentiated to yield a point estimate and a 95% CI for the ratio of the ratios.

8.2 Additional Effectiveness Endpoints Analyses

The ITT Population will be the primary analysis population for the secondary effectiveness endpoints.

8.2.1 Subject Satisfaction at 24 Weeks

A chi-square test of goodness of fit will be performed, assuming expected cell counts are the same for both ReCell and Control.

8.2.2 POSAS – 24 Week Observer Overall Opinion Score

The treatment difference of the Observer overall opinion score will be assessed by a two-sided paired t-test with $\alpha = 0.05$, as well as the confidence interval.

8.2.3 POSAS – 24 Week Patient Overall Opinion Score

The treatment difference of the Patient overall opinion score will be assessed by a two-sided paired t-test with $\alpha = 0.05$, as well as the confidence interval.

8.3 Other Analyses

For the analyses described below, statistical significance will be declared if $p \leq 0.050$ for a two-sided test. There will be no adjustment for multiplicity for these supportive analyses. Unless otherwise indicated.

8.3.1 Treatment Area Closure Assessment by Blinded Evaluator

The ReCell and control treatment areas will be assessed for closure (i.e., healing) by a Blinded Evaluator at all study visits (blinded assessment). Categorical data for healing (i.e., 100%, 80-99% etc.) will be presented by treatment area by visit. A score ranging from 1 to 5 will be assigned to categories, with a larger score representing greater healing.

The proportion of treatment areas that have achieved each degree of wound healing at each follow-up visit, based on the Blinded Evaluator's assessment, will be summarized by treatment. The difference in the distribution of the wound healing categories between treatments will be assessed by a Wilcoxon matched-pairs signed-ranks test for ordered data.

8.3.2 Treatment Area Closure Assessment by Non-Blinded Evaluator

The ReCell and control treatment areas will be assessed for closure (i.e., healing) by a Non-Blinded Evaluator at all study visits (non-blinded assessment) using the same assessment tool and statistical analyses described for the Blinded Evaluator.

8.3.3 Long-term Wound Appearance – POSAS Scores

Individual components of both the Observer and Patient Assessment of the POSAS, and Total POSAS scores, and the POSAS overall opinion ratings will be summarized descriptively (number of subjects, mean, median, standard deviation, minimum, maximum) by visit and

treatment. A paired t-test will be used for comparison between the two treatments, and two-sided 95% confidence intervals will be presented for the difference in means for each treatment.

8.3.4 Blinding Effectiveness

Blinded Evaluator and Subject blinding effectiveness assessments data will be summarized by treatment using counts and percentages for each response identified; i.e., ReCell, Control, or Unsure. No statistical analyses will be performed.

8.3.5 Subject Satisfaction

Subject satisfaction will be summarized by treatment using counts and percentages for each assessment interval.

8.4 Inter-rater Reliability

The degree of agreement between the unblinded and blinded investigator's assessment of wound healing at Week 8 will be calculated for each of the two study treatment sites using McNemar's test.

9.0 SAFETY ANALYSES

The Safety population will be used for all safety analyses.

Adverse events will be coded using the Medical Dictionary for Regulatory Activity (MedDRA), version 18.0 terminology for data summaries. Each adverse event will be coded with 2 levels including Preferred Term (PT) and System Organ Class (SOC). Adverse events will also be tabulated by severity and relationship to the device.

An overview summary table of AE will be prepared including the number of subjects and percentage of subjects reporting an AE for the following categories:

- Subjects reporting at least one AE
- Severity of AEs (Mild, Moderate, Severe)
- Subjects reporting at least one device -related AE
- Subjects reporting at least one Serious AE
- Subjects with AE resulting in death on study

The number and percentage of subjects with the following categories of AEs will be summarized overall and for each location by SOC and PT:

- Any AE
- Any AE by severity
- Any AE by relationship to device

The ReCell and Control Adverse events will be compared using a McNemar's test.

The following dichotomous safety outcomes will be summarized by treatment using counts and percentages.

- Delayed Healing
- Infection
- Allergic response to trypsin
- Wound durability, in terms of recurrent wound breakdown following initial complete closure
- Scars necessitating surgical intervention

9.1 Additional Safety Analyses

9.1.1 Subject Assessment of Pain at Treatment Area

Treatment area pain will be assessed using the Subject Pain Assessment and the Pain Score from the Patient Assessment scale of the POSAS. Pain scores will be summarized by visit and by treatment descriptively (number of subjects, mean, median, standard deviation, range). Paired t-test will be used to test the difference between the two treatments by study visit and for the confidence interval. Nominal P value (unadjusted) will be presented.

9.2 Other Analyses

9.2.1 Retreatment

Treatment areas requiring retreatment will be summarized with counts and percentages. Details for retreatments will be included in a listing. The date between initial treatment and retreatment will be calculated and presented.

10.0 QUALITY CONTROL

All data displays and analyses will adhere to the International Conference on Harmonization (ICH) *Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (ICH Topic E3).*

All analyses will be performed using SAS® Version 9.3 (or later). Advanced Clinical will follow its standard operating procedures in the creation and quality control of all tables, listings, figures, and analyses. Avita or its designee will review all tables, listings, and figures prior to final database lock. All final SAS programs and associated output files will be transferred to Avita in agreed-upon format at project completion.

11.0 TABLE AND LISTING CONVENTIONS

Mock-ups for statistical tables and data listings will be provided. Final formats for the statistical tables and listings may deviate from these mock-ups upon agreement with the Sponsor. Footnotes will be used as needed to clarify the information that is presented in the tables and listings. Unless otherwise requested by the Sponsor, the term ‘subject’ will be used in all tables and listings, in accordance with Clinical Data Interchange Standards Consortium (CDISC) standards.

The general layout of tables and listings will be as follows:

Avita Medical, Inc. Page x of y

Protocol: CTP001-7 Run Date: DDMMMYY-HH:MM

Clinical Study Report

Listing 16.2_x (or Table 14.x_x)

<Title>

<Population>

Col 1 Col 2 Col 3 etc.

<Any footnotes>

File Name: <pathname for SAS program>

All tables and listings will use landscape orientation. Margins will be at least 2.0 cm at the top and bottom and at least 0.8 cm on the left and right, excluding headers and footers, in accordance with electronic Common Technical Documents (eCTD) guidelines. Font will be Courier or Courier New, unless otherwise specified, with a 10-point font size in most cases. Page numbering will be sequential within each table, listing, and figure. Column headers should be in initial capital letters. Units for numeric data will be included when appropriate.

Unless otherwise requested by the Sponsor, the derivation of relative study day will follow CDISC standards. The first day of study agent administration will be Day 1, with a negative sign indicating the number of days prior to the first day of study agent administration (e.g., Day -1 is the day prior to first administration of the study drug agent). There will be no Day 0.

Tables and data listings will be created from different SAS programs. A single program may produce multiple tables or multiple data listings from the same dataset (e.g., all clinical chemistry data listings may be generated by a single program).

Statistical Table Conventions

Mock-ups for statistical tables will include headers, title numbers, titles, column headers and footers, and a proposed layout for the display of data. The final decision on the precision (i.e., number of decimal places) for presentation of descriptive statistics will be made by the Sponsor after review of draft statistical tables and before database lock.

Data Listing Conventions

Mock-ups for data listings will include headers, title numbers, titles, column headers, and footers. Data listings will provide all data either collected on the corresponding CRF page or loaded directly into the database, unless otherwise indicated. If there are too many fields to be fit

into a single page, data should be grouped logically and the listings will be generated as Part I, Part II, etc.

In general, data listings should include all subjects with data. However, if only subjects who meet a certain condition are listed (e.g., subjects with SAEs) and no subjects meet the condition, the data listing will so indicate.

The data presented in data listings will be sorted by subject number. Where appropriate, data will be sorted by subject number and treatment. Within a subject, data will be listed in chronological order. Whenever possible, formatted values will be displayed (i.e., decoded). Where applicable, calendar date and study day of evaluations/events will be provided in the data listings.