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)

Investigational Plan

Study Number:	CTP006-2
Device:	RECELL® Autologous Cell Harvesting Device
Study Type:	Pivotal Study
IDE Reference Number:	13053
Issue Date/Version:	December 11, 2020 / Revision 5
Sponsor:	AVITA Medical Americas, LLC 28159 Avenue Stanford, Suite 220 Valencia, CA 91355

PRINCIPAL INVESTIGATOR'S STATEMENT

This statement is to certify that I have received the above-referenced investigational plan, which has been approved for initiation at my investigational site by the Institutional Review Board. As Principal Investigator, I will ensure that all personnel who have been delegated responsibilities for this study will be trained on the investigational plan and associated responsibilities prior to study participation. I agree to conduct this clinical study in compliance with the investigational plan and applicable requirements of the U.S. Code of Federal Regulations (21 CFR Parts, 50, 54, 56, 812 and 45 CFR Part 46).

Print Name: _____
Principal Investigator

Signature: _____ Date: _____
Principal Investigator

PROTOCOL SYNOPSIS

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)
Protocol No.	CTP006-2
Sponsor	AVITA Medical Americas, LLC 28159 Avenue Stanford, Suite 220 Valencia, CA 91355
Funding	Funded by the Biomedical Advanced Research and Development Authority (BARDA) within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services
Investigational Treatment	Application of RES® prepared using the RECELL® Autologous Cell Harvesting Device to partial-thickness burns (dressed with Telfa™ Clear primary and Xeroform™ secondary wound dressings)
Control Treatment	Mepilex® Ag Wound Dressing (Mölnlycke Health Care) is a standardly employed dressing for second-degree/partial-thickness burns due to its non-adherent and antimicrobial properties. The layered dressing includes a flexible, absorbent polyurethane foam pad embedded with silver sulfate compound and vapor permeable film backing with a silicone layer covered with a polyethylene release film.
Phase of Study	Pivotal Study
Proposed Indication for Use	The RECELL Device is indicated for treatment of partial-thickness burns in patients 1 year of age or greater.
Primary 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.
Planned Enrollment	To evaluate the primary endpoint, enrollment of **160 subjects** is planned. This study utilizes an adaptive design with interim analysis for early stopping due to futility or positive outcome and, if necessary, sample size re-estimation in order to maintain adequate condition power. The maximum enrollment will be **300 subjects**.
Trial 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. <u>Primary Effectiveness Assessments</u>: 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. An interim analysis will be conducted after approximately 50% of total enrollment has reached the primary effectiveness endpoint (i.e., 80 subjects have completed the primary endpoint evaluation including confirmation of healing at Day 28). 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 at most 300 subjects. Safety data will be reviewed and adjudicated by an Independent Medical Monitor. A Data Monitoring Committee 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.
Number of Trial Centers	Up to 25 US trial centers with a specialty in pediatric burn care will participate. No center will contribute more than 25% of the total randomized subjects without written Sponsor permission.
Duration of Participation	Each subject will participate in the trial for 52 weeks post-treatment.
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. The hypothesis to be evaluated is whether the incidence of Day 10 healing post-treatment is greater (superior) with RECELL treatment vs. Control treatment.
Safety Endpoints	Safety will be evaluated in terms of treatment-related adverse events and serious device-related adverse events.
Secondary Effectiveness Endpoints	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 Endpoints/ Data Collection	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/CMS-1500 and/or similar hospital and physician claim forms for billing purposes to collect data associated with the initial hospital care and readmissions during follow-up as applicable). 9. Index Burn Itch Man Scale ratings.
Pre-Randomization Inclusion Criteria	1. Male or female patients aged 1 through 16 years (inclusive) with a partial-thickness thermal burn injury. 2. The patient has a thermal burn injury that is: a. ≤ 30% TBSA (exclusive of superficial areas) and b. ≤ 10% TBSA is a full-thickness burn. 3. The Index Burn must be a clean partial-thickness burn injury ≥160 cm^2 and between 2-20% BSA (inclusive). 4. The Index Burn may not cover the face, hand, foot or the perineum/genitalia (Note: a patient with wounds in these areas may be enrolled but the Index Burn Area may not include these areas). 5. The patient and/or parent/guardian agrees to comply with all compulsory study procedures and visit schedule. 6. The patient and/or parent/guardian agrees to abstain from any other treatment for closure of the Index Burn for the duration of the study unless medically necessary. 7. The patient and/or parent/guardian agrees to abstain from enrollment in any other interventional clinical trial for the duration of the study. 8. In the opinion of the investigator, the patient and/or parent/guardian must be able to: a. Understand the full nature and purpose of the study, including possible risks and adverse events, b. Understand instruction, and c. Provide voluntary informed written consent/assent as appropriate for study participation.
Pre-Randomization Exclusion Criteria	1. Not able to understand English or Spanish. 2. Burns caused by chemicals, electricity or radiation. 3. Patients presenting with only 3rd-degree/full-thickness wounds which require immediate autografting. 4. Burn injury has had prior treatment for definitive closure. 5. Patients for whom use of sedation/general anesthesia is not medically appropriate. 6. Superficial/trivial burns or burns that in the investigator's opinion appear to be healing sufficiently such that care under this protocol would be inappropriate. 7. Patient requires immediate or staged surgical procedures for closure of their partial-thickness burns. 8. Conditions, e.g., previous burn injury to study area, poor nutritional status, poorly controlled diabetes mellitus (HbA1c >9%), that in the investigator's opinion may compromise subject safety or trial objectives. 9. Current use of medications, e.g., immunosuppressive agents (excluding inhaled corticosteroids), that in the investigator's opinion may compromise subject safety or trial objectives. 10. Inhalation injury. 11. Active infection, cellulitis or need for immediate grafting at the planned treatment areas. 12. Concerns for parent/guardian's ability to provide appropriate follow-up care. 13. Subjects with a known hypersensitivity to trypsin or compound sodium lactate for irrigation solution. 14. Subjects with a known sensitivity to silver.

	15. In post-pubescent girls, pregnant or breast-feeding (pregnancy test should be performed in accordance with local institutional requirements). 16. Immediate life-threatening condition or life expectancy less than one year. 17. Previous randomization within this investigation.
Post-Randomization (Prior to treatment) Eligibility Criteria	Post-Randomization Inclusion: 1. Patient randomized (and will be treated) within 72 hours from the time of the burn injury. 2. Patient continues to meet all pre-randomization inclusion criteria. Post-Randomization Exclusion: 1. Incidental finding of any pre-randomization exclusion criteria. Consented subjects who do not meet the post-randomization eligibility criteria and did not receive study treatment will be followed through the Day 28 visit and then withdrawn from the study. The criteria for which exclusion was based will be documented.
Statistical Considerations	Based on medical input, the estimated proportion of subjects with confirmed 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. 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. A formal unblinded interim analysis comparing treatments on the primary endpoint will be conducted once 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). 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 patients with available primary endpoint data; there will no imputation of missing data at this interim analysis. The Intent to Treat (ITT) population will consist of all enrolled subjects who are randomized, with data analyzed according to randomized treatment assignment. The Modified Intent to Treat (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. Per Protocol (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.

	The primary effectiveness endpoint 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 for closure (including conventional autografting) prior to the Day 28 visit, this will be considered an endpoint failure.