A Prospective Multicenter Randomized Controlled Clinical Study to Investigate the Safety and Effectiveness of the RECELL® System Combined with Meshed Autograft for Reduction of Donor Skin Harvesting in Soft Tissue Reconstruction

Investigational Plan

Study Number:	CTP007
Device:	RECELL® Autologous Cell Harvesting Device
Study Type:	Pivotal Study
IDE Reference Number:	13053
Date:	October 30, 2020 / Revision 2
Sponsor:	AVITA Medical 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 the RECELL® System Combined with Meshed Autograft for Reduction of Donor Area in Soft Tissue Reconstruction
Protocol No.	CTP007
Phase of Study	Pivotal Study
Intended Use	The RECELL® Autologous Cell Harvesting Device is indicated for use in combination with meshed autografting for treatment of acute full-thickness skin defects such as degloving, crush, laceration (including pretibial), and surgical wounds (e.g., flap donor, skin cancer resection, post-debridement for cellulitis or infection).
Primary Objective	To evaluate the safety and effectiveness of the RECELL Device when used as an adjunct to meshed autografts in patients undergoing reconstruction of skin defects not associated with a burn injury.
Planned Enrollment	A minimum of **65 subjects** will be enrolled and randomized in the study to evaluate the coprimary endpoints. This study utilizes an adaptive design with planned sample size re-estimation in order to maintain adequate conditional power. The maximum enrollment will be **126 subjects.**
Number of Trial Centers	Up to 20 trial centers in the United States (US) may participate.
Clinical Justification/Benefit	Use of RECELL as an adjunct to autografts meshed more widely than conventional meshed autografts will allow for reduction in donor skin harvesting required for autografting. Donor site morbidity, including pain, infection and delayed healing, are reduced for smaller donor areas; therefore, reduction of donor skin harvesting offers clinical benefit.
Investigational Treatment	Skin cell suspension prepared using the RECELL Device will be applied over autografts meshed more widely than a standardized comparator.
Control Treatment	Conventional autografting
Study Design	This is a prospective randomized within-subject, blinded evaluator, multicenter controlled study to compare the clinical performance of conventional autografting with and without skin cell suspension on acute nonburn full-thickness skin defects. Patients with a total body surface area (TBSA) acute skin defect up to 50% (inclusive) will be considered for participation in this study. An autografting plan for closure of the skin defect will be developed and documented in accordance with investigators' standard of care. Two comparable contiguous or non-contiguous areas, each at least 80 cm^2 in size will be identified as study treatment areas and labeled as Area A and Area B. These areas will be randomly assigned to autografting treatment consistent with the Investigator's pre-identified and documented autograft plan (Control) or to receive RECELL treatment in combination with an autograft meshed more widely than identified in the pre-specified autograft plan. For example, if the autografting plan calls for a 2:1 meshed autograft, this will form the Control and will be compared to an area treated with 3:1 meshed autograft and RECELL. The donor site(s) for skin harvested for the RECELL and Control treatments will be measured (area, cm^2) and documented. The two study treatment areas will be compared with respect to healing characteristics, the amount of donor skin harvesting required and safety-related adverse events. Treatment-area healing will be evaluated via direct visualization by the treating investigator (unblinded) and by a qualified clinical study team member blinded to

	treatment allocation (i.e., Blinded Evaluator). The blinded assessment will serve as the primary healing assessment. Donor expansion associated with treatments, and incidence of healing, will be evaluated 8 weeks after treatment for the purposes of a regulatory application (PMA supplement) for market approval of RECELL for this clinical indication. During the regulatory phase of the study, there will be follow-up visits at 1, 2, 4, 6, 8, 10, 12 and 26 weeks to evaluate the safety and effectiveness of RECELL for this indication, with durability confirmed at Week 26. Treatment-related and serious adverse events will be reported through Week 26. Participants will be seen for longer-term follow up at Weeks 36 and 52 to collect additional longer-term outcome data for publication. During the early assessments, the preferred method is in-person clinical visits, however (if necessary), the follow-up visits may be conducted remotely (e.g., via telemedicine) with the exception of Week 8 and the confirmation of healing visit. At all visits, subjects' study treatment areas will be documented photographically using standardized digital photography. Scar outcomes will be evaluated using the Patient and Observer Scar Assessment Scale (POSAS) questionnaire, which includes components for both the Blinded Evaluator and the subject. Subjects will be asked which treatment area they are more satisfied with (prior to unblinding), and then after unblinding, they will be told how much donor skin was associated with each treatment and the question of treatment preference will be asked again. Data from this clinical investigation will be summarized in a Clinical Study Report (CSR) and presented to the Food and Drug Administration (FDA) once all subjects have completed their Week 26 visit. All available data, including Week 52, for subjects who have completed the study at that time will be included in the report. The CSR will be amended once all subjects have completed the study
Co-primary Effectiveness Endpoints	• Healing at (or prior to) 8 weeks post-treatment. Healing is defined as complete closure characterized by 100% skin re-epithelialization without drainage, confirmed at two consecutive study visits at least 2 weeks apart by direct visualization by a Blinded Evaluator. The incidence of healing is hypothesized to be non-inferior for RECELL-treated areas as compared to Control areas. • 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 separately for RECELL and Control (including donor skin needed for secondary treatments). The actual expansion ratios will be compared as a new ratio (ratio of ratios). The actual expansion ratio achieved with the use of RECELL is hypothesized to be superior to the actual expansion ratio associated with the Control.
Safety Evaluations	Safety will be evaluated in terms of long-term durability, scar outcomes and treatment-related adverse events. Safety variables that will be compared between the two treatments are: 1. Delayed healing/non-healing 2. Infection 3. Allergic response to trypsin 4. Treatment area durability 5. Scar outcomes for which surgical intervention is determined to be medically necessary 6. Pain 7. Treatment-related and serious adverse events

Additional Data Collection	1. Investigator's (unblinded) assessment of healing at study treatment areas and donor site(s) 2. Scar outcomes reported by the Blinded Evaluator and patient (blinded) using the POSAS. 3. Effectiveness of treatment blinding for the Blinded Evaluator at Week 8. 4. Effectiveness of treatment blinding for the subject at Week 26. 5. Subject (or parent/guardian) treatment preference at Week 52. 6. Investigator treatment preference at Week 52.
Inclusion Criteria	Subjects must meet all the following criteria to be eligible for participation: 1. The patient requires autografting for treatment of an acute full-thickness skin defect (e.g., trauma- or surgery-related). 2. The maximum area requiring autografting is 50% TBSA. 3. Two comparable areas requiring autografting, each at least 80 cm^2 (or 160 cm^2 contiguous), excluding face and genitalia. When hands, feet or joints are included in the treatment areas, comparability of treatment areas means that each area (RECELL and Control) must include the same contralateral joint and/or hand/foot. 4. The patient is at least 5 years of age. 5. The patient (or parent/guardian) is willing and able to comply with all compulsory study procedures and visit schedule. 6. The patient (or parent/guardian) agrees to abstain from any other treatment of the study areas for the duration of his/her participation in the study (1 year). 7. The patient agrees to abstain from enrollment in any other interventional clinical trial for the duration of his/her participation in the study (1 year). 8. In the opinion of the investigator, the patient and/or guardian must be able to: a) Understand the full nature and purpose of the study, including possible risks and adverse events, b) Understand instructions, and c) Provide voluntary written informed consent.
Exclusion Criteria	Subjects who meet any of the following criteria are not eligible for participation: 1. Not able to understand English or Spanish. 2. The area requiring autografting sustained a burn injury. 3. The treatment area has previously failed to heal subsequent to surgical intervention for closure. 4. The patient is unable to follow the protocol requirements. 5. The patient has a condition that in the investigator's opinion may compromise patient safety or trial objectives. 6. Current use of medications that in the investigator's opinion may compromise patient safety or trial objectives. 7. The patient has a known hypersensitivity to trypsin or compound sodium lactate for irrigation (Hartmann's) solution. 8. The patient is pregnant or breast-feeding (pregnancy test should be performed in accordance with local institutional requirements). 9. Life expectancy is less than 1 year.

Study-specific procedure highlights	• The study treatment areas will be prepared using standard surgical techniques. • The surgeon will identify and document an autografting plan for areas to be autografted [i.e., identifying areas to receive sheet graft, minimally perforated graft, and meshed graft (1:1, 2:1, 3:1)]. • Subsequent to development of the autografting plan, two comparable treatment areas (with similar plans) will be identified as study treatment areas A and B by either bisecting one contiguous area or identifying two similar non-contiguous areas and photographed after appropriate demarcation with a surgical marker. • The randomization envelope is opened to identify which area (A or B) is Control and which is RECELL. • The autografting plan is followed as originally documented for the area assigned to Control • The originally documented autografting plan is amended as follows for the area assigned to RECELL: ▪ Sheet, minimally perforated or 1:1 will instead be 2:1 mesh and RECELL ▪ 2:1 mesh will instead be 3:1 mesh and RECELL ▪ 3:1 mesh will instead be 4:1 mesh and RECELL • Donor site(s) for skin allocated to RECELL and Control study treatment areas will be measured (area, cm^2) and documented.
Statistical Considerations	The sample size was determined so as to provide at least 80% probability that both co-primary endpoints will be met. Primary effectiveness will be assessed on the following two analysis sets: Intent to treat population (ITT) – All those enrolled into the study who are randomized; and Per protocol population (PP) – ITT subjects who receive both study treatments and have no major protocol deviations. The hypotheses to be tested for the co-primary endpoint of Confirmed Healing is the proportion of RECELLtreated autograft area healed prior to or at the 8-week visit is non-inferior to the standard of care Control treated graft area. For the co-primary effectiveness endpoint for confirmed treatment area closure, the hypothesis test of non-inferiority will be one-sided with a 2.5% significance level; for the endpoint of relative reduction in donor site area, the hypothesis test of superiority 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. An unblinded conditional power calculation and sample size re-estimation will be conducted once approximately 50% of total enrollment has been evaluated for the primary effectiveness endpoint; i.e., 33 subjects have been randomized and reached the Week 8 visit (or healing confirmatory visit) or would have reached the Week 8 visit had they not prematurely withdrawn. To account for missing data and/or loss of subjects from the PP analysis population, the sample size was increased to 65 patients which represents an attrition rate of approximately 10%.