A Prospective Blinded Within-Subject Randomized Controlled Clinical Study to Investigate the Safety and Effectiveness of RECELL for Repigmentation of Stable Vitiligo Lesions

Investigational Plan

Study Number:	CTP009
Device:	RECELL® Autologous Cell Harvesting Device
Study Type:	Pivotal Study
Date / Revision:	July 8, 2021 / Rev 4
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

1.0 PROTOCOL SYNOPSIS

Title	A Prospective Blinded Within-Subject Randomized Controlled Clinical Study to Investigate the Safety and Effectiveness of RECELL for Repigmentation of Stable Vitiligo Lesions
Protocol No.	CTP009
Phase of Study	Pivotal Study
Proposed Indication for Use	The RECELL® Autologous Cell Harvesting Device is intended for use at the patient's point-of-care for the safe and rapid preparation of Spray-On Skin™ Cells from a small sample of a patient's own skin. The cell suspension prepared using the RECELL System is suitable for application to a prepared treatment area for repigmentation of stable vitiligo lesions.
Primary Objective	To evaluate the application of Spray-On Skin™ Cells, prepared using the RECELL® Device, for safe and effective repigmentation of ablated stable vitiligo lesions.
Study Population	<u>Pivotal Cohort</u> The pivotal cohort will consist of no fewer than **23 subjects**. This study utilizes an adaptive design with an interim analysis planned for the purposes of sample size re-estimation (to achieve adequate conditional power). There will be a maximum of **46 subjects** in the pivotal cohort. <u>Roll-in Cohort</u> Up to two roll-in cohort patients may be randomized at each investigational site for purposes of ensuring proficiency with the investigational device and study procedures prior to advancing to enrollment in the pivotal cohort. Any subject randomized prior to Rev 3 of the investigational plan will be considered a roll-in cohort subject. All roll-in subjects must meet the same eligibility criteria, will undergo the same study procedures and follow-up assessments as the pivotal cohort subjects; however, data from the roll-in cohort of subjects will be analyzed separately from the pivotal cohort. A maximum of **35 subjects** total roll-in cohort subjects (including those randomized prior to Rev 3) are anticipated in addition to the planned pivotal cohort subjects. Subjects in the roll-in cohort may not re-enroll in the pivotal cohort. There will be a maximum of **81 subjects** from both cohorts.
Number of Trial Centers	The study will be executed at no more than 15 centers in the United States.
Clinical Justification/Clinical Benefit	The RECELL® Autologous Cell Harvesting Device has been safely and effectively used to prepare and apply cell suspension that includes pigment-producing cells (melanocytes) for treatment of burn wounds. Patients without functional melanocytes and who are candidates for application of skin cells to depigmented areas of skin may benefit from point of care use of the RECELL Device.
Investigational Treatment	Skin cell suspension at 1:20 expansion ratio (donor area : recipient area), prepared using the RECELL System, will be applied to an ablated (de-epithelialized) area of depigmentation, followed by targeted phototherapy using NB-UVB.
Control	Each subject will serve as their own Control, with a depigmented area receiving no RECELL treatment but receiving the same targeted NB-UVB as the investigational treatment area.

Study Design	This is a prospective blinded randomized within-subject controlled study to evaluate the clinical performance of RECELL for repigmentation of stable, depigmented lesions in subjects 18 years or greater. The trial will evaluate matched pairs of stable depigmented study areas. After identification of two study areas, one study area will be randomly assigned to RECELL, and the other will serve as the Control. Follow-up visits during the effectiveness period will be at Weeks 1, 4, 12 and 24 post-treatment followed by a durability period that will include follow-up visits at Weeks 36 and 52 post-treatment. Acute healing, pigmentation, and compliance with phototherapy will be evaluated. Treatment-related and serious adverse events will be documented throughout the duration of the study. For all study subjects and visits, study areas will be documented using standardized digital photography. Pigmentation of all study areas will be determined via centralized image interpretation by an expert dermatological panel blinded to treatment allocation (i.e., Central Review Committee, CRC) to decrease variability. In addition to the CRC, an assessment of pigmentation and study area Vitiligo Area Scoring Index (VASI) will be performed by the investigator for each study area. To assess durability of responding RECELL-treated study areas at Week 52, the investigator and the CRC will confirm that ≥ 80% of the pigmentation remains relative to the subject's Week 24 photograph. Patient reported outcomes will be captured using the Vitiligo Noticeability Scale (VNS), Patient Global Impression of Change-Vitiligo (PaGIC-V), and a subject global treatment success assessment. After completion of the Week 24 (non-responders) or Week 52 (responders) visit, the subject may be given the option for RECELL treatment of their depigmented study area(s).
Primary Effectiveness Endpoint	The primary effectiveness endpoint is the proportion of Responders for RECELL-treated areas versus Control at Week 24. Responders are defined as study areas achieving ≥ 80% pigmentation as determined by the Central Review Committee.
Secondary Effectiveness Endpoints	1. Central Review Committee categorization of repigmentation (0-25%, 26-50%, 51-79% and 80-100%) at Week 24 2. Central Review Committee assessment of color matching for the study areas at Week 24
Tertiary (Exploratory) Measures	1. Subject and investigator global treatment success and donor site satisfaction 2. Subject-reported Vitiligo Noticeability Score vs baseline (based on photographs) 3. Investigator assessment of pigmentation responder (≥ 80% pigmentation) for the study areas at Week 24 4. Investigator assessment of repigmentation category (ordinal data) for the study areas 5. CRC and investigator assessment of pigmentation for the study areas at Weeks 36 and 52 6. Investigator study area VASI scores, change from baseline 7. Investigator assessment of color matching for the study areas 8. CRC assessment of color matching for the study areas at Weeks 36 and 52 9. Patient Global Impression of Change-Vitiligo (PaGIC-V) 10. Repigmentation durability at Week 52 as assessed by the investigator and CRC

Safety Evaluations	Safety will be evaluated in terms of healing and scar outcomes, and treatment-related adverse events. Safety variables that will be evaluated at the study areas and donor sites: 1. Incomplete healing (<100%) at Week 4 2. Infection 3. Koebnerization 4. Donor and recipient site scar requiring surgical treatment 5. Milia requiring medical intervention 6. Other treatment-related and serious adverse events
Inclusion Criteria	Subjects must meet all the following criteria to be eligible: 1. Focal, segmental or generalized (i.e., nonsegmental) stable vitiligo, defined as no new depigmented areas nor any depigmented areas that have expanded in size within the preceding 12 months, regardless of whether the areas are intended to be used as study areas. 1a. Photo documentation (current and at least 12 months prior) of the patient's depigmented areas have been evaluated as stable by an independent Screening Committee. 2. The patient has not undergone topical treatment (e.g., steroids, tacrolimus) for the study areas within the past 90 days. 3. The patient has not undergone phototherapy (e.g., NB-UVB) for the study areas within the past 90 days. 4. The patient is a candidate for surgical intervention of a depigmented area, defined as a patient who has previously been compliant with but has not satisfactorily responded to both: a. topical therapy *and* b. a minimum of 3 months of phototherapy. 5. The patient must have two study areas available for treatment that: a. are of similar size (±50%), b. are between 16cm^2 and 456cm^2 (contiguous), c. are similarly sun exposed, d. have the same extent of leukotrichia, and e. are judged clinically as ≥90% depigmented (by area). 6. The patient is 18 years of age or older. 7. The patient is willing and able to comply with post-treatment at-home phototherapy and all follow-up evaluations required by the study protocol. 8. The patient agrees to abstain from any other treatment of the study areas for the duration of his/her participation in the study (52 weeks). 9. The patient agrees to abstain from enrollment in any other interventional clinical trial for the duration of his/her participation in the study (52 weeks). 10. In the opinion of the investigator, the patient 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: 1. The study areas selected have concomitant dermatologic conditions other than vitiligo. 2. The study area selected for treatment includes the lips, eyelids, plantar surface of feet, palmar surface of hands, fingertips, wrists, ankles, elbows, or knees. 3. The patient is unable to undergo the treatment area preparation. 4. Patients who are pregnant. 5. Patients with any of the following: a. universalis vitiligo, b. depigmented areas over >30% of their body surface area, c. depigmented lips and fingertips (lip-tip vitiligo), or d. > 3 depigmented fingertips, defined as depigmentation of the dorsal aspect of the fingertip from the distal interphalangeal joint to the tip of the digit. 6. Patients with recent history (within previous 12 months) of: a. Koebnerization, b. confetti-like, or c. trichrome lesions. 7. Patients with a history of keloid formation. 8. Patients who have used a tanning salon in the past 60 days. 9. The patient has other concurrent conditions that in the opinion of the investigator may compromise patient safety or study objectives. 10. Current use of medications (e.g., anticoagulants such as heparin or warfarin) that in the investigator's opinion may compromise patient safety or trial objectives. 11. The patient has a known hypersensitivity to trypsin or compound sodium lactate for irrigation (Hartmann's) solution. 12. Life expectancy is less than 1 year.
Study-specific procedure highlights	• Two depigmented study areas will be outlined and labeled (A and B). • Randomization to assign area A or B to RECELL will be performed in the EDC. • Donor skin will be harvested under local anesthetic sufficient to prepare suspension for both the recipient and donor sites. • The RECELL-assigned study area will be ablated to a sufficient depth to remove the epidermis and expose the papillary dermis. • Spray-On Skin™ Cells will be applied to the RECELL-assigned study area using a 1:20 expansion ratio. • Standardized dressings will be applied to the RECELL-treated study area and donor site. • NB-UVB phototherapy will commence on both study areas after dressings are no longer in place.

Screening Committee (SC)	Post-consent and prior to randomization, investigational sites must submit photographic evidence (with date stamp or other evidence of date of image acquisition) of stable vitiligo for each subject that includes: 1) Current photos of the subject's depigmented areas obtained during screening 2) Current photos of the subject's dorsal hands displaying all fingertips obtained during screening 3) Historic photos ≥ 12 months prior of the subject's depigmented areas The independent SC will consist of a minimum of 3 board-certified dermatologists. Each patient being considered for treatment will have the photographic evidence outlined above in addition to other relevant medical history reviewed by a minimum of 3 committee members. Two (2) of 3 members must concur the photographs are of stable vitiligo prior to the investigational site proceeding with randomization and treatment. The SC will be blinded to which investigational site the photographs originated from.
Central Review Committee (CRC)	Three independent board-certified dermatologists (Central Review Committee, CRC) will be selected based on specific selection criteria for the purpose of providing blinded adjudication to determine whether successful repigmentation of the study areas (≥ 80%) have been achieved and if not, then to determine categorization of repigmentation. The CRC will be blinded to the study site, treatment assignment, and the investigator's determination of repigmentation for each study area. The adjudicated results will be used in the primary analysis. The CRC will be governed under a charter that will be approved by the committee, and that will contain the guidance and rules under which they will review and adjudicate data. Assessments of repigmentation at 24 weeks post- treatment (relative to baseline) will be assessed by all three members of the CRC. If two CRC members agree, adjudication of that subject's timepoint will be deemed complete. If there are any discordant cases (i.e., agreement not achieved between two CRC members), the committee will review the case together with the majority ruling (2/3 CRC members in agreement) serving as the final adjudication. The CRC members will record their review independently. Panel assessments will be conducted consistent with consensus guidance published by the Vitiligo Global Issues Consensus Group (VGICG) for the evaluation of patients with vitiligo using a reference atlas developed by the VGICG depicting vitiligo repigmentation patterns and color match.

Statistical considerations	The sample size for this trial was determined based on the primary effectiveness endpoint of responders at 24 weeks. The trial is designed to test if RECELL treatment using an expansion ratio of 1:20 is superior to Control. An alpha level of 0.025 is utilized for hypothesis testing. The trial will incorporate an unblinded interim analysis for purposes of sample size re-estimation after approximately half the planned subjects reach 24 weeks. The interim analysis will be conducted according to the promising zone method of Mehta and Pocock (2011), allowing for up to twice the original planned sample size. Assuming 5% responders in Control and 60% responders for RECELL, 20 subjects yields 90% power, one-sided 0.025 level of significance to demonstrate RECELL superiority versus Control. This assumes a 10% superiority margin relative to Control. Anticipating 10% lost to follow-up, 23 subjects are planned. An interim analysis for purposes of sample size re-estimation will occur when 11 subjects have 24-week follow-up data. The sample size may be increased based on the results of this interim analysis to a maximum of 46 subjects. Note that it is possible that, depending on rate of subject accrual, the interim analysis of 24-week data may not occur until after 23 subjects have already been enrolled.