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Reconstructive

Open-label Venous Leg Ulcer Pilot Study Using a Novel Autolologous Homologous Skin Construct

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Background: Venous leg ulcers (VLUs) are often refractory to compression therapy, and their prevalence is increasing. An autologous homologous skin construct (AHSC) that uses the endogenous regenerative capacity of healthy skin has been developed to treat cutaneous defects, with a single application. The ability of AHSC to close VLUs with a single treatment was evaluated in an open-label, single-arm feasibility study to test the hypothesis that AHSC treatment will result in wound closure by providing healthy autologous tissue to the wound bed.

Methods: Ten VLUs were treated with a single application of AHSC. A 1.5 cm^2 full-thickness skin harvest from the proximal calf was collected and sent to a Food and Drug Administration–registered facility, where it was processed into AHSC and returned to the provider within 48 hours. AHSC was spread evenly across the wound and dressed with silicone. The primary endpoint was wound closure rate at 12 weeks. Wound closure was followed with 3-dimensional planimetry, and closure was confirmed by a panel of plastic surgeons. Additional endpoints followed for 12 weeks included graft take, harvest site closure, adverse event rate, complications, and patient-reported pain.

Results: All 10 VLUs demonstrated successful graft take as evidenced by graft persisting in wound and harvest site closure. Eight VLUs exhibited complete closure within 12 weeks. One VLU that failed to heal with a prior split thickness skin graft closed within 13.5 weeks with AHSC. The mean time of closure was 34 days (95% confidence interval, 14–53). Pain improved by closure confirmation visit. There was 1 serious adverse event unrelated to the product or procedure.

Conclusion: This pilot study demonstrated that AHSC may be a viable single-application topical intervention for VLUs and warrants further investigation in larger, controlled studies. *(Plast Reconstr Surg Glob Open 2020;8:e2972; doi: 10.1097/GOX.0000000000002972; Published online 16 July 2020.)*

INTRODUCTION

Venous leg ulcers (VLUs) are among the more common types of chronic wounds, occurring in >2% of the general population and costing $14.9 billion each year.[1–3] Several advanced wound care therapies, including biological skin substitutes such as placental membranes, acellular tissue matrices, and cultured biosynthetic dressings, are commercially available for the treatment of VLUs.[4–6] Although studies demonstrate that some of these therapies may offer a significant clinical benefit when used as an adjunct to compression therapy for treating

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VLUs, they often require multiple applications such as the weekly application seen in recent allogeneic tissue studies, which escalates treatment costs.[7–13]

An autologous homologous skin construct (AHSC) has been developed for the repair and replacement of skin.[14–17] It is created from a small harvest of healthy full-thickness skin, which is sent to an FDA-registered manufacturing facility. AHSC manufacturing creates microaggregates, retaining the endogenous regenerative and support cell populations that are responsible for skin repair.[14,15] AHSC processing optimizes the aggregates for passive diffusion and activates endogenous pathways involved in skin repair in a physiological media void of enzymes or growth factors. It is not cultured ex vivo but rather returned to the provider in a syringe and can be spread evenly across the wound bed, where the native wound environment supports the autologous aggregates. These implant and expand within the wound, facilitating closure by constructing both matrix and epithelium.[15,17] An early clinical case of AHSC application demonstrated its ability to close a chronic lower extremity wound that was previously refractory to multiple split-thickness skin grafts.[14] The ability of AHSC to close VLUs with a single treatment was evaluated in an open-label, single-arm feasibility study to test the hypothesis that AHSC treatment will result in wound closure by providing healthy autologous tissue to the wound bed.

PATIENTS AND METHODS

Study Design and Population

This open-label, single-arm pilot study took place from November 6, 2018, to August 13, 2019, at a single outpatient wound clinic. The objective of this study was to treat 10 patients with VLUs to evaluate the ability of a single application of AHSC used in the office setting to close VLUs. The primary endpoint was wound closure rate at 12 weeks. Additional endpoints included the AHSC take rate at 12 weeks, the harvest site closure rate at 12 weeks, occurrence of adverse events (AEs; defined as any untoward event that happened to the subject beginning with the harvest procedure), complications (defined as any deviation from the normal treatment course), and patient-reported pain during the harvest procedure, application procedure, and follow-up visits, based on a Visual Analogue Scale of 0–10. The product was provided at no cost by the manufacturer. The cost of AHSC per VLU was estimated using the manufacturer's standard price.

No sample size calculation was used in this pilot study. The sample size for this exploratory study was set at 10 adult patients with a VLU, so that their data could be used in the design of a future randomized controlled trial (RCT) that has since begun enrolling (NCT03881267).

The inclusion criteria for this study included persons at least 18 years old with a VLU on the leg (below the knee and above the aspect of the medial malleolus) that extended at least through the dermis or subcutaneous tissue without involving tendon, muscle, or bone and that had a clean, granular base that was free from necrotic debris and appeared to be healthy vascularized tissue at the time of AHSC placement. The index ulcer had been present for at least 4 weeks before AHSC treatment. Exclusion criteria included patients with known allergies to the components of the multilayer compression bandaging or who could not tolerate multilayer compression therapy and if the index ulcer was suspicious for cancer or that had a local, active, soft-tissue infection or gangrene. Eligible patients who provided their written informed consent were enrolled into the study. This study was conducted according to the principles expressed in the Declaration of Helsinki, and the Western Institutional Review Board (Puyallup, Wash.) approved the study protocol. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines were followed.

AHSC Harvest and Application Procedures and Follow-up

All harvest and application procedures were performed in an outpatient wound care clinic. The patient's clinical and wound history was recorded before the harvest procedure. Sterile technique was used to excise a 1 cm × 2 cm elliptical full-thickness skin harvest from a healthy area of skin of the proximal calf of the affected limb of each subject using local anesthesia. Harvest sites were closed primarily, covered with an antibiotic ointment, and covered with a nonadherent dressing, which was covered by the compression dressing. This location for the harvest was chosen because (1) some providers may have limitations in harvest site locations above the knee in a wound care clinic setting; (2) the proximal medial calf is often unaffected by complications of venous leg insufficiency; and (3) the harvest site can be covered by the same compression dressing as the index ulcer, reducing the amount of dressing care needed by the patient. The harvest was mailed overnight to a Food and Drug Administration–regulated biomedical manufacturing facility (PolarityTE Inc., Salt Lake City, Utah), where the tissue was used to manufacture the AHSC (SkinTE, PolarityTE Inc.; Salt Lake City, Utah) The AHSC was returned to the clinic within 48 hours of tissue harvest and applied to the wound bed 3–4 days after the harvesting procedure per provider's discretion for scheduling purposes.

At the time of AHSC application, the wound was sharply debrided of necrotic tissue. All of the provided AHSC was spread evenly across the wound bed and covered with silicone dressing, bolstered by an absorbent foam (DermaFoam; DermaRite, North Bergen, N.J.), and covered by a 3-layer compression bolster (DYNA-FLEX; KCI and Acelity, San Antonio, Tex.). The closed harvest site was covered by the 3-layer compression bolster. Patients were observed, and dressings were changed weekly until closure confirmation visit. Patients were informed to elevate the index limb. The silicone dressing was replaced by a nonadherent contact layer (Adaptic Touch; Acelity, San Antonio, Tex.) at the third dressing change and covered as aforementioned, which was continued until the VLU

was confirmed closed. Patients were followed up until wound closure.

At each visit, the provider assessed graft take by visual confirmation of AHSC in the wound bed, wound measurements (Insight; eKare Inc., Fairfax, VA), harvest site closure, index and harvest wound infection assessed clinically and confirmed by the need for antibiotic therapy, and patient-reported pain. A VLU was deemed closed if it remained completely epithelialized without drainage 2 weeks after it was first determined to be closed by the treatment provider and was confirmed by consensus of a blinded adjudication panel comprising plastic surgeons by reviewing the high-resolution digital photography.

Data were analyzed by a statistician (Strategic Solutions Inc., Cody, Wyo.). Descriptive statistics were used to analyze patient and wound characteristics and pain data. Percent in wound area reduction for all wound was calculated at 4 weeks. A Kaplan–Meier analysis was used to analyze time-to-close with 95% confidence interval (CI).

The product cost of AHSC was analyzed using the manufacturer's pricing. Constructs with an area of ≤5 cm^2 cost $950, >5 cm^2 but ≤10 cm^2 cost $1600, and >10 cm^2 but ≤20 cm^2 cost $2200.

RESULTS

Ten patients (5 men, 50%) with a mean age of 66 years (SD, 10; range, 51–78) were consecutively screened and enrolled into the study. Table 1 details the patient and wound characteristics. Nine patients (90%) were white, and 1 (10%) patient was Hispanic. Their mean body mass index was 35 (SD, 8; range, 24–46). The patients had multiple comorbidities (mean, 7; SD, 3; range, 3–12), and 8 (80%) patients had type II diabetes. Eight patients' VLUs had a known duration of a mean 15 weeks (SD, 14; range, 4–47). Their mean initial wound area was 4 cm^2 (SD, 4; range, 1.3–12.2).

All 10 patients underwent a single harvest and a single application procedure. All harvest sites were successfully closed at the time of harvest and remain closed throughout the study. Graft take was observed in all wounds. Eight patients' VLUs closed within 4 weeks (Fig. 1). Patient No. 3 had a 12.2 cm^2 VLU that had been open for 11 months and had not responded well to a prior split-thickness skin graft (STSG). This wound closed after 13.5 weeks after one graft of AHSC therapy. Therefore, a total of 9 wounds achieved complete closure. The VLU of patient No. 9 closed at day 27 postapplication, but it reopened before the closure confirmation visit as a result of a whitewater rafting incident. Figure 2 shows the Kaplan–Meier time-to-closure curve. The mean time to closure was 34 days [standard error (SE), 10; 95% CI, 14–53]. The median time to closure was 21 days (SE, 3; 95% CI, 15–27). Nine patients had wound area data recorded at 4 weeks; the mean percent in wound area reduction for these 9 patients was 100%. There were no index wound infections requiring antibiotic therapy.

There was 1 serious AE, which was unrelated to the study product or procedure. Patient No. 6 had diabetes and was hospitalized for a spinal abscess involving vertebral osteomyelitis with methicillin-resistant *Staphylococcus aureus* 3 weeks following AHSC application. Interventional radiology drained the abscess, and the patient received 6 weeks of vancomycin for the osteomyelitis. The patient returned to the study clinic on week 4 with a closed VLU. No further complications were reported.

Table 1. Characteristics of Patients and Wounds

Patient No.	Age, y	Race	Sex	BMI	Comorbidities	Duration of Ulcer, wks	Ulcer Location	Initial Wound Area, cm^2	Time to Closure, days
1	51	W	M	46	Hypertension, hyperlipidemia, BFN, hypothyroidism, CHF, GERD, type II diabetes, depression, bilateral venous insufficiency	6	Right shin	2.7	25
2	63	W	F	42	Hypertension, BFN, CKD, type II diabetes, Charcot foot	8	Left calf	1.3	18
3	71	W	F	29	Hypertension, GERD, arthritis, multiple sclerosis, anxiety, depression	47	Left calf	12.2	92
4	77	W	F	29	Hypertension, hyperlipidemia, BFN, type II diabetes, anemia	4	Left shin	2.9	19
5	78	W	F	29	Hypertension, hyperlipidemia, BFN, hypothyroidism, depression, GERD, type II diabetes, diabetic foot ulcer, bunion, hammertoes	6	Left shin	3.3	14
6	67	W	M	35	Hypertension, BFN, lower extremity edema, chronic back pain, type II diabetes	13	Left shin	2.4	27
7	75	H	M	24	BFN, CHF, type II diabetes	21	Right calf	1.9	25
8	59	W	M	41	Hypertension, hyperlipidemia, BFN, hypothyroidism, restless leg, type II diabetes, anemia, myasthenia gravis, depression, anxiety, enlarged prostate, venous stasis	>4	Posterior, left calf	8.9	21
9	67	W	F	31	Depression, venous stasis, current smoker	13	Left calf	2.4	Unhealed
10	52	W	M	44	Hypertension, hyperlipidemia, BFN, depression, GERD, type II diabetes, edema, venous stasis, current smoker, chronic pain	Many (exact duration unknown)	Right, medial ankle	2.5	4

BFN, bilateral foot neuropathy; BMI, body mass index; BPH, benign prostatic hyperplasia; CHF, congestive heart failure; CKD, chronic kidney disease; F, female; GERD, gastroesophageal reflux disease; H, Hispanic; W, White.

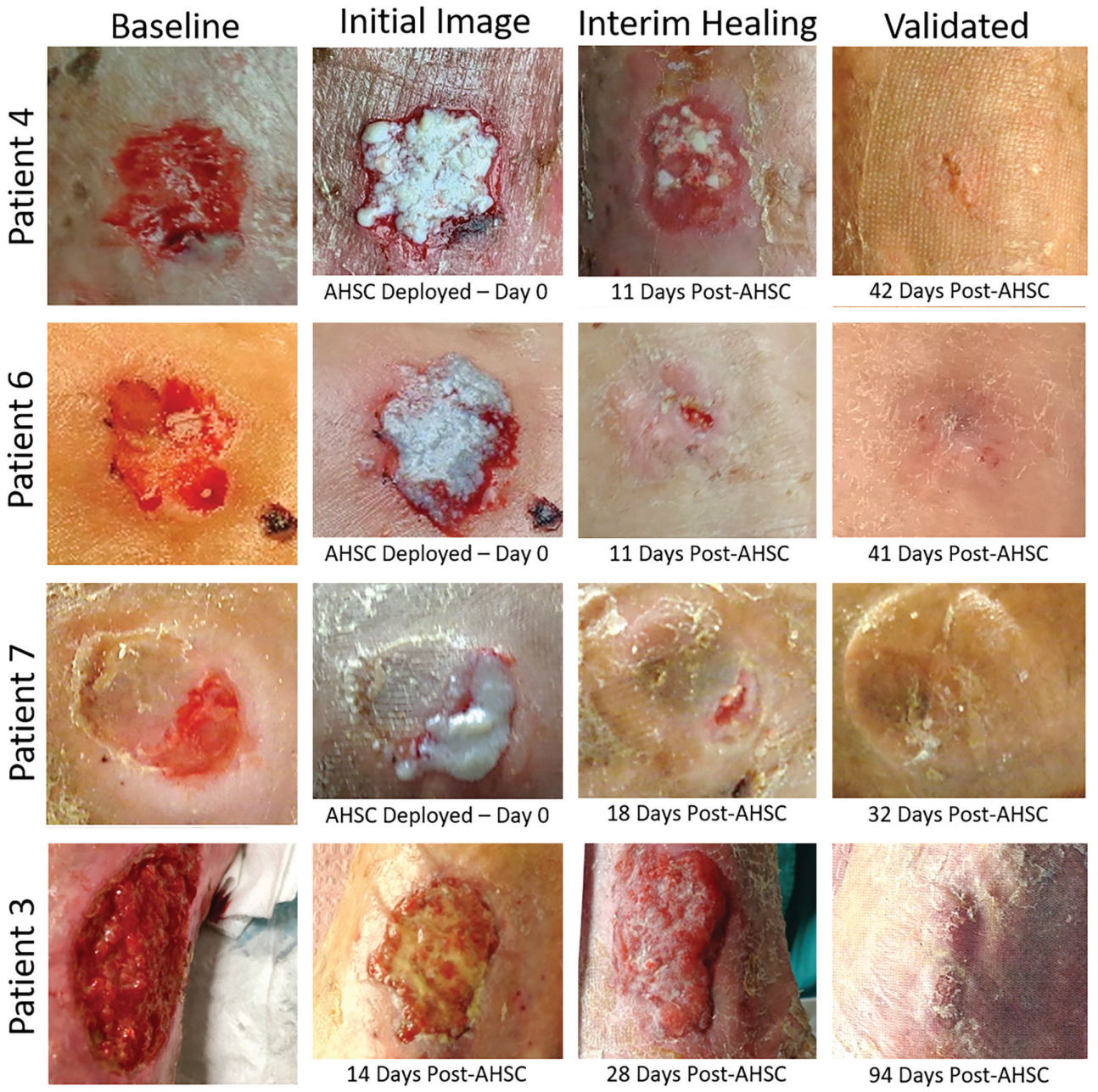

Fig. 1. Representative images of progressive closure of AHSC-treated VLUs. Patient 3 had a VLU that was present for over 7 months, that had previously failed to heal with a split thickness skin graft, after a single application of the AHSC the wound achieved closure at 13.5 weeks.

Table 2 summarizes patient-reported pain. The mean pain reported during the harvest procedure was 4 (SD, 2), which decreased to 3 (SD, 2) during the application procedure. Pain was nonexistent to mild (0–2) from the follow-up visits through the closure confirmation visit. The mean calculated product cost to close a VLU during this study was $1140 (SD, $420), and the median cost was $950.

DISCUSSION

This pilot study evaluated the ability of a novel AHSC treatment to completely close VLUs with a single application in the setting of an outpatient wound clinic. Nine chronic VLUs (90%) closed after a single application of AHSC; 8 closed within 4 weeks, and 1 complex wound closed within 13.5 weeks. One additional VLU closed within 4 weeks but reopened shortly after initial closure was observed. All harvest site wounds remained closed without complications, and graft take was observed in all wounds. One adverse event/serious adverse event (AE/SAE) occurred (AE rate, 10%), which was unrelated to the product or procedure. No further complications with the treatment or harvest sites were reported, and minimal

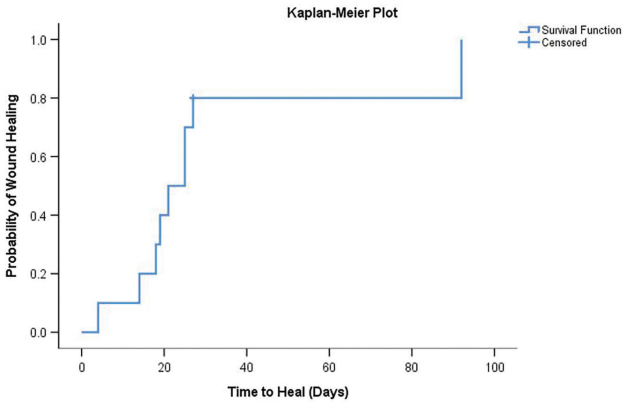

Fig. 2. Kaplan–Meier time-to-close graph. The mean time to closure was 34 days [standard error (SE), 10; 95% CI, 14–53]. The median time to closure was 21 days (SE, 3; 95% CI, 15–27). Nine patients had wound area data recorded at 4 weeks; the mean PAR (percent in wound area reduction) for these 9 patients was 100%.

Table 2. Summary of Patient-reported Pain during Course of Study, Based on a VAS of 0–10

Study Visit	No. of Patients Reporting Pain (%)	Mean VAS (SD)	Range
Harvest	10 (100%)	4 (2)	0–6
Application	10 (100%)	3 (2)	0–7
Week 1	10 (100%)	2 (2)	0–7
Week 2	8 (80%)	2 (3)	0–7
Week 3	8 (80%)	1 (2)	0–5
Week 4	7 (70%)	1 (1)	0–2
Week 5	2 (20%)	0.5 (1)	0–1
Week 6	1 (10%)	1 (NA)	NA
Week 7	1 (10%)	1 (NA)	NA
Week 8	1 (10%)	2 (NA)	NA
Week 9	1 (10%)	2 (NA)	NA
Week 10	1 (10%)	1 (NA)	NA
Week 11	1 (10%)	0 (NA)	NA
Week 12	1 (10%)	1 (NA)	NA
Week 13	1 (10%)	0 (NA)	NA
Closure confirmation	9 (90%)	1 (1)	0–3

NA, not applicable; VAS, Visual Analogue Scale.

pain was reported (Table 2) throughout the study. These findings suggest that AHSC may be a safe and viable treatment for chronic VLUs. This study is limited by its small sample size, lack of a control arm, open-label design, and retrospective reporting. Additionally, the VLUs were relatively small, and all patients received compression therapy in addition to the AHSC treatment. These promising results will be evaluated in a larger RCT (NCT03881267).

VLUs develop and chronically persist due chronic trauma, vascular insufficiency, and chronic inflammation in the wound environment.[18] Treatment with standard multilayer compression dressings and advanced dressings such as amniotic membranes and allogenic cellular skin substitute rely upon the epithelium at the wound margin to proliferate and close the wound from the outside-in. An appreciable rate of failure is seen with these approaches in part because these therapies are dependent on cellular proliferation within the compromised wound bed.[8,19–21] Skin grafts provide healthy tissue to a wound bed that can incorporate and facilitate closure. However, the metabolic demands of the transferred tissue during the early engrafting period may not be met by the chronic wound bed, which is attributed to the increased failure rate of STSG in VLU treatment.[22–26] Skin grafting also requires an operating room and highly trained staff that increases the cost of chronic wound care and is usually not performed in outpatient-based wound care practices.[27–29] Furthermore, in a peri- and post–coronavirus disease 2019 (COVID-19) environment, efforts to reduce the use of inpatient/operating room resources as much as possible has taken on even a greater urgency.[30]

An advantage of an autologous tissue-based therapy like AHSC is that it is created from a piece of healthy unaffected skin and then transferred to the wound bed, contributing fresh cells and tissue similar to a skin graft. Unlike a split-thickness skin graft, AHSC is created from full-thickness skin and retains the potent endogenous regenerative populations found within the dermis. AHSC treatment has been shown to result in skin with full-thickness architecture, including sweat glands and hair follicles.[14,15] Additionally, the high surface area-to-volume ratio of AHSC facilitates the survival of AHSC cellular populations via plasmatic imbibition before they take onto the wound bed and revascularization occurs. Thereafter, AHSC expands within the wound bed to close the wound from an inside-out manner independent of the compromised peri-wound skin.

In this pilot study, AHSC treatment was able to completely close the VLUs with a single application. By contrast, in one cohort study involving cryopreserved, human skin allograft and allogenic cellular skin substitute, an average of 2.3 and 3.3 applications, respectively, were required.[10] Another study determined that 3 applications of allogenic cellular skin substitute were needed to close a VLU.[8] This study was not designed to compare with other products, and these other studies may have different patient parameters influencing the product costs. However, the single application of the AHSC may result in reduced treatment costs. An RCT underway (NCT03881267) will bear more information regarding the cost-effectiveness of the AHSC treatment.

This study demonstrated that AHSC is a viable single treatment for chronic VLUs refractory to standard compression therapy. Additional studies are warranted to further evaluate these findings.

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SkinTE is an autologous, homologous, FDA-registered, cutaneous human cellular and tissue-based product (HCT/P) that can be used as an adjunct to standard of care, for skin coverage in patients who have suffered from a venous leg wound in conjunction with standard wound care. Use of SkinTE on venous leg wounds in this study was done in compliance with homologous

use by the FDA under Section 361 of the PHS Act and 21 CFR Part 1271. The commercially available tissue is minimally manipulated and processed at an FDA-registered facility; it is placed as a replacement for skin on the venous leg wounds to promote skin healing. This trial was funded by the PolarityTE and was approved by the Western Institutional Review Board, Pullup, Wash. (WIRB Protocol Number: 20191456 STE-02).

Site investigators and the principal investigator were financially compensated for their time involved in conducting this trial using research funds. Each investigator filled out a conflict of interest form with the IRB. Although Western IRB does not consider receiving research funds to conduct a trial as a conflict of interest, no individual with an actual conflict, as defined by the Western IRB, was permitted to consent or participate in the management of any patient in this trial.

All authors attest to the ICMJE guidelines state that "authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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