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Demonstration of the safety and effectiveness of the RECELL® System combined with split-thickness meshed autografts for the reduction of donor skin to treat mixed-depth burn injuries

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ARTICLE INFO

Article history:
Accepted 8 November 2018
Available online xxx

Keywords:
RECELL
RECELL® System
Burns
Skin graft
Autograft
Mixed-depth burns
Full-thickness burns
Autologous skin cell suspension
Spray-On Skin™ cells

ABSTRACT

Introduction: Split-thickness skin grafts (STSG) are the standard of care (SOC) for burns undergoing autografting but are associated with donor skin site morbidity and limited by the availability of uninjured skin. The RECELL® Autologous Skin Harvesting Device (RECELL® System, or RECELL) was developed for point-of-care preparation and application of a suspension of non-cultured, disaggregated, autologous skin cells, using 1 cm^2 of the patient's skin to treat up to 80 cm^2 of excised burn.

Methods: A multi-center, prospective, within-subject controlled, randomized, clinical trial was conducted with 30 subjects to evaluate RECELL in combination with a more widely meshed STSG than a pre-defined SOC meshed STSG (RECELL treatment) for the treatment of mixed-depth burns, including full-thickness. Treatment areas were randomized to receive standard meshed STSG (Control treatment) or RECELL treatment, such that each subject had 1 Control and 1 RECELL treatment area. Effectiveness measures were assessed and included complete wound closure, donor skin use subject satisfaction, and scarring outcomes out to one year following treatment.

Results: At 8 weeks, 85% of the Control-treated wounds were healed compared with 92% of the RECELL-treated wounds, establishing the non-inferiority of RECELL treatment for wound healing. Control-treated and RECELL-treated wounds were similar in mean size; however, mean donor skin use were significantly reduced by 32% with the use of RECELL ($p < 0.001$), establishing the superiority of RECELL treatment for reducing donor skin requirements. Secondary effectiveness and safety outcomes were similar between the treatments.

Conclusions: In combination with widely meshed STSG, RECELL is a safe and effective point-of-care treatment for mixed-depth burns without confluent dermis, achieving short- and long-term healing comparable to standard STSG, while significantly decreasing donor skin use.

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https://doi.org/10.1016/j.burns.2018.11.002

1. Introduction

Every year in the United States (US), half a million burn injuries occur. Treatment of these patients is dictated by the severity of the insult, with smaller superficial burns treated most often on an outpatient basis with conventional dressings; whereas, deeper and more extensive injuries typically undergo hospitalization for proper management [1–3]. The most common approach for treating severe burns is early excision of the burn and prompt closure. Use of autologous split-thickness skin grafts (STSG) is considered standard of care (SOC) treatment to achieve definitive closure. However, this treatment strategy is associated with significant pain, pruritus, infection, dyschromia, dyspigmentation, delayed healing, and hypertrophic scarring [4,5]. Due to these complications and the known acute morbidity associated with effectively increasing the total body surface area (TBSA) of open wounds by creating donor sites, burn autografting is carefully considered with the intent to achieve timely healing while limiting the amount of skin harvested.

The RECELL® Autologous Skin Cell Harvesting Device (RECELL® System, AVITA Medical, Valencia, CA, US) was developed to minimize the amount of healthy skin to achieve definitive closure of burn injuries. The concept is based on the work of Stoner and Wood and the recognition that immediate autologous transplantation of a population of individual skin cells without laboratory culture could offer long-term wound closure in a clinically advantageous time-frame while optimizing patient outcomes [6]. Using the RECELL® System, an autologous skin cell suspension (ASCS) is prepared from an autograft 0.006–0.008 inches thick at the point-of-care and is applied immediately to an excised wound bed, with every 1 cm^2 of donor skin yielding 1 ml of suspension that covers up to 80 cm^2 of treatment area.

Following application, the ASCS induces rapid epidermal regeneration achieving re-epithelialization to heal burns [7,8], STSG donor sites [9], chronic wounds [10,11], hypopigmented scars [12], vitiligo [13,14], and large congenital melanotic nevi [15]. A randomized study by Gravante et al., showed that deep partial-thickness (DPT) burns treated with ASCS produced by RECELL had similar results to standard autografting, while using significantly less donor skin and being associated with significantly less donor site pain [7].

Furthermore, a recently published multi-center, prospective, within-subject controlled, randomized clinical trial further demonstrated these results for DPT burns [16]. This study evaluated definitive wound closure outcomes when applying ASCS compared with 2:1 meshed STSG for the treatment of DPT burns, within a population of 101 subjects with 1–20% TBSA acute thermal burns. Both treatments were clinically effective in healing >97% of the treated burns by Week 4 (98% for ASCS and 100% for STSG). A 98% reduction in donor skin was found for the RECELL-treated wounds with improved healing for the RECELL donor skin site compared to the STSG donor skin site at 1 and 2 weeks, as well as improved RECELL donor site pain, subject satisfaction, and scarring outcomes.

In the randomized clinical studies by Holmes et al. and Gravante et al, ASCS prepared using RECELL retains the known performance attributes of a STSG, while minimizing donor skin use to achieve definitive closure of DPT thermal burns and donor site morbidity [7,16]. The purpose of the clinical trial described herein was to evaluate the safety and effectiveness of ASCS prepared using RECELL in combination with a STSG meshed more widely (RECELL treatment) than a SOC conventional STSG (Control treatment) for the treatment of mixed-depth, inclusive of full-thickness, acute thermal burns covering 5–50% TBSA in a patient population equal to or greater than 5 years of age. Application of ASCS as a stand-alone treatment was not evaluated for the treatment of the mixed-depth burns in this study, as it is only indicated for direct, stand-alone application to wounds containing confluent dermis. However, as a meshed autograft is indicated for these deeper injuries and is currently considered SOC, an evaluation of the combination was undertaken, with the aim of reducing the amount of donor skin taken for complete closure without compromising healing.

2. Materials and methods

2.1. Study design

This was a multi-center, prospective, evaluator-blinded, within-subject controlled, randomized clinical trial conducted under a US Food and Drug Administration (FDA) Investigational Device Exemption (ClinicalTrials.gov Identifier: NCT02380612). For each subject, following burn excision, 2 comparable contiguous or non-contiguous areas were treated according to random assignment, resulting in a Control area receiving STSG consistent with the Investigator's pre-identified SOC grafting plan (Control treatment) and a treatment area to which ASCS was applied over STSG more widely meshed by a factor of 1 than specified in the pre-identified SOC graft plan (RECELL treatment). Following treatment, subjects were followed over a 52-week period, and all study wounds were photographically documented. Prior to study initiation, the protocol was approved by the Institutional Review Boards (IRBs) at each individual study site.

2.2. Subject selection

Subjects aged 5 years or older were eligible for study enrollment, if they presented with an acute thermal burn involving 5–50% of TBSA that underwent autografting for definitive closure. Subjects must have had 2 areas with autografting, each at least 300 cm^2 (or 600 cm^2 contiguous). To minimize variability amongst the SOC autografting regimens across the multiple centers, burns involving the face, hands, feet, and joints were excluded as treatment areas. Additional exclusion criteria included burns caused by chemicals, electricity, and/or radioactive substances; inability of the patient to follow the protocol; other concurrent conditions that in the opinion of the investigator might compromise subject safety or study objectives; a known hypersensitivity to trypsin or compound sodium lactate (Hartmann's) solution; and a life expectancy of <1 year.

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2.3. Wound bed preparation

The burn injuries were excised to remove all non-viable tissue, hemostasis was achieved, and 2 treatment areas similar in size (within ±20%) and severity of injury were marked Area "A" and Area "B" using a sterile marker. Wound areas were measured and documented.

2.4. Standard of care grafting plan — control treatment designation

The investigators documented their SOC grafting plans based on the extent of the injury and available donor sites. Although often only one meshing ratio was planned, up to 3 different meshing ratios were allowed and selected from the following 5 options: sheet graft, minimally perforated ("pie crust"), 1:1, 2:1, and 3:1. Multiple meshing options within a given Control treatment area were permitted because the use of multiple meshing ratios could be especially appropriate in larger burns.

2.5. Randomization

Within-subject allocation of treatments to selected burn wounds was performed at random, using a pre-determined assignment of treatments. Areas A and B were randomized to receive either STSG consistent with the investigator's pre-identified SOC grafting plan (Control Treatment) or ASCS applied over STSG more widely meshed by a factor of 1 than specified in the pre-identified graft plan (RECELL treatment).

2.6. Donor skin harvesting

The STSG used for treatment of the Control area was meshed according to the pre-identified graft plan. The STSG used for treatment of the area allocated to RECELL was meshed more widely (2:1, 3:1, or 4:1). Thinner donor skin (0.006″–0.008″) for the preparation of ASCS using RECELL was either harvested separately or trimmed from skin harvested for the meshed STSG. The total area of donor sites for the initial STSG, as well as for any re-treatments, were measured, documented, and compared between Control and RECELL treatments.

2.7. STSG treatments

For both Control and RECELL-treated wounds, the meshed STSG was maintained in saline moistened gauze until placement on the excised wound bed. Following application to the wound bed, the STSG was secured in place using either staples or sutures at the surgeon's discretion.

2.8. ASCS application

The RECELL® System was used per the manufacturer's instructions for burns randomized to RECELL treatment. A skin sample (1 cm^2 per 80 cm^2 of intended treatment area) was incubated for 15–20 min in a warmed proprietary enzyme solution (RECELL® Enzyme) to breakdown adhesions between cells and the extracellular matrix, including dermo-epidermal junction adhesions. After removal from this Enzyme solution and placement on the device's sterile tray, the skin sample was tested to determine if the epidermis and dermal tissue could be freely separated. When this was possible, buffer solution was used to rinse the skin sample; after which, the skin sample was placed dermal side down on the device's sterile tray. The skin sample was completely disaggregated by vigorously scraping both the dermal and epidermal layers. The disaggregated skin cells were suspended in a buffer solution, filtered, drawn into the application syringe, and applied over the more widely meshed STSG on the RECELL wound area. Telfa™ Clear Wound Dressing (Covidien, Minneapolis, MN) was applied to the inferior margin of the wound before proceeding with ASCS application. The cell suspension was sprayed on the wound from the most elevated part to the least elevated part, so that run-off waste was minimized. One ASCS application was delivered to the entire surface of the wound. Finally, the Telfa™ Clear Wound Dressing was wrapped over the treated site and secured in place.

2.9. Post-operative care

The Control-treated area was also covered with Telfa™ Clear Wound Dressing. For both treatment wounds, a secondary dressing of Xeroform™ Occlusive Petrolatum Gauze Dressing (Covidien) was placed over the primary dressing, and additional padding of gauze and a crepe bandage were used at the surgeon's discretion for exudate absorption and protection. The use of silver-impregnated dressings was prohibited.

The Telfa™ Clear primary dressing remained in place for a minimum of 6–8 days and was not manipulated until the first post-operative study visit, unless medically necessary. Beginning at 48 h after treatment, secondary dressings were changed every other day for review of the treated areas and were replaced as appropriate. Secondary dressings were replaced with silver-impregnated dressings if there was concern for infection (e.g. — malodorous or excessively moist areas). If the malodorous or moist area resolved, silver-impregnated dressings were replaced with Xeroform™ Occlusive Petrolatum Gauze dressings. If a suspected infection was microbiologically confirmed or clinically worsened, the affected area was debrided and treated topically or systemically, as appropriate.

Subsequent to re-epithelialization, the treated areas were protected for a minimum of 2 weeks using light hydrophobic compression garments/sleeves or dry gauze and elastic bandaging along with continued use of Xeroform™ dressings, as needed. Vigorous cleansing or excessive application of topical creams was avoided to prevent damaging the newly formed skin.

Thereafter, post-operative care was consistent with the SOC for the clinical site.

2.10. Study endpoints

The co-primary effectiveness endpoints were (1) confirmed treatment area closure (i.e., healing) prior to or at Week 8, defined as complete skin re-epithelialization without drainage, confirmed at 2 consecutive study visits at least 2 weeks apart by direct visualization by an Investigator blinded to treatment assignment and (2) comparison of the actual

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expansion ratios, computed as the ratio of measured treated area to measured area of the donor site, achieved for the Control and RECELL treatment areas. The area of the donor site included donor skin for the initial treatment, as well as any re-treatments. A ratio of ratios was calculated as the RECELL expansion ratio:Control expansion ratio.

Secondary endpoints were assessed at Weeks 12, 24, 36, and 52 and included subject satisfaction measured by asking the subjects to specify which treatment regimen was more satisfactory and assessments using the Patient and Observer Scar Assessment Scale (POSAS), including blinded observer and patient total score and overall opinion score.

2.11. *Safety assessments*

Safety evaluation included comparison of rate and severity of treatment-related adverse events (TRAEs) including device-related events and serious events, and the following pre-specified selected safety events: delayed healing (not healed by Week 8 after the initial treatment per investigator assessment and not undergoing surgical intervention), infection, allergic response to trypsin (component of RECELL® Enzyme), wound durability as determined by incidence of recurrent wound breakdown following initial complete closure, and scars necessitating surgical intervention. Additional safety events were also evaluated including subject assessment of pain at treatment area (based on a pain scale of 1–10, where 1 represented no pain and 10 represented worst possible pain) and skin graft failure.

Adverse events (AEs) were coded using MedDRA, Version 18.0 and tabulated overall and by severity and relationship to the RECELL® System. Adverse events were summarized by location (Control wound, RECELL wound, and non-study location [i.e., neither Control nor RECELL treatment areas]). Additionally, descriptive statistics were provided for the following safety variables: delayed healing, infection, allergic response to trypsin, wound durability, scars necessitating surgical intervention, treatment area pain, and skin graft loss.

2.12. *Statistical methods*

The study was designed to investigate the clinical performance of RECELL relative to Control STSG, for the treatment of mixed-depth burn injuries (inclusive of full-thickness). Co-primary effectiveness endpoints were to test non-inferiority of the incidence of RECELL-treated site closure by Week 8 when compared with that of the Control, and the superiority of the relative reduction in donor skin for the RECELL treatment when compared with that of the Control.

A sample size of 25 subjects (50 observations) provides 81.3% power for the first co-primary effectiveness endpoint (confirmed treatment area closure by the 8 week visit), based on non-inferiority testing (with a 10% non-inferiority margin) evaluating the proportion of subjects with wound closure by the 8 week visit in a paired design with one area of burn wound treated with RECELL and one area of burn wound treated with conventional autografting, using a one-sided test, $\alpha=0.025$, assuming the true proportion (%) for RECELL is 98% and the true proportion for conventional autografting (i.e., the control) is 100%. The true proportion for the control is assumed to be 100%, and therefore constant, which means that the covariance between the outcome for the control and the outcome for RECELL for a given subject equals 0, thereby reducing the test statistic of the paired design to the test statistic for a parallel group design.

At 25 subjects, the power for the second co-primary effectiveness endpoint (ratio of donor expansion ratios) exceeds >99.9%, with a superiority comparison of RECELL to control in a paired design, using a one-sided test, $\alpha=0.025$, and assuming true distribution of 1.59 (70%), 1.33 (15%), and 1.17 (15%).

The probably of meeting both co-primary endpoints exceeds 80%. Let A=reject the null hypothesis in favor of the alternative hypothesis for both co-primary endpoints and B=reject the null hypothesis for the second co-primary endpoint.

Then $P(A \text{ and } B)=P(A)+P(B)-P(A \text{ or } B)$

$\geq P(A)+P(B)=1>0.813+0.999-1>0.812>0.80$

To account for missing data and loss of subjects the sample size was increased to 30, which represents an attrition rate of approximately 15%.

For the co-primary effectiveness endpoint of confirmed treatment area closure by Week 8, the hypothesis test of non-inferiority was evaluated by a 97.5% one-sided confidence interval (97.5% CI) for the difference in the proportion of subjects with confirmed treatment closure on or before Week 8 based on a non-inferiority margin of 10%. For non-inferiority to be established, the upper limit of the 97.5% CI for the difference (Control minus RECELL) between treatments had to be less than 10%.

For the co-primary effectiveness endpoint of relative reduction in donor skin, the hypothesis test of superiority was one-sided with a 2.5% significance level. To establish the superiority of RECELL to Control, the geometric mean ratio (GMR) of expansion ratios (RECELL:Control) had to be >1, and the associated p-value had to be ≤0.05. All other statistical tests for effectiveness endpoints were two-sided at the 5% significance level.

Study populations were defined as (1) intent-to-treat population (ITT) consisting of all enrolled subjects who had their treatment areas randomized; (2) per-protocol population (PP) consisting of ITT subjects who received both study treatments in accordance with the randomization, completed primary endpoints visits, and had no major protocol deviations; and (3) safety population consisting of all enrolled subjects who received treatment with RECELL.

The statistical analysis of the data obtained from the study was conducted by an independent third-party (Advanced Clinical, Deerfield, IL) using SAS Version 9.3. Continuous variables were summarized using descriptive statistics, specifically, the mean, median, standard deviation, minimum, and maximum. Categorical variables were summarized by frequencies and percentages.

3. Results

Between January 2015 and February 2017, 1029 subjects were assessed for eligibility. A total of 999 subjects were excluded, and 30 subjects were enrolled in the study at 6 burn centers

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within in the US. Comparison between the 2 treatments included SOC Control treatment meshing ratios from 1:1–3:1, with a breakdown of 1:1 meshed Control treatment compared to 2:1 meshed RECELL treatment (n=7), 2:1 meshed Control treatment compared to 3:1 meshed RECELL treatment (n=19), and 3:1 meshed Control treatment compared to 4:1 meshed RECELL treatment (n=5). One subject received STSGs with multiple meshing ratios for both Control and RECELL treatment areas. Of the 30 subjects enrolled, all had treatment areas randomized, received both treatments per randomization, and were included in the ITT and safety populations. Twenty-six subjects received both treatments, completed their primary endpoints visits, and had no major protocol deviations and were included in the PP population (Fig. 1).

The mean subject age was 39.1±15.8 years, while 83% of the subjects were male and 67% of the subjects were White (Table 1). The majority of burns (73.3%) were fire/flame-related injuries. Burn injury occurred between 1 to 55 days prior to the day of study treatment. The mean TBSA affected by burns was 21±13%, with a mean total estimated area with grafting of 2443±1675 cm^2 (Table 2).

Table 1 – Demographics and comorbidities.

Safety population (N=30)	
Age (years)	
Mean±stdev	39.1±15.8
(Range)	(9.0-68.0)
Sex (% male)	83%
Race (%)	
Black or African American	20.0%
Asian	3.3%
White	66.7%
Other	10.0%
Risks for impaired wound healing	
None	70.0%
Current smoker	26.7%
Inadequate nutrition	3.3%
Other	3.3%

3.1. *Treatment area closure by Week 8*

Wound closure was evaluated from Week 4 through Week 12, and the proportion of subjects with confirmed wound closure was similar between treatments at all time points (Fig. 2). At Week 4, approximately 50% of the subjects achieved complete wound closure (48% for Control compared with 50% for RECELL). By Week 6, approximately 80% of the subjects achieved complete wound closure (74% for Control compared with 78% for RECELL). At Week 8 in the PP population (primary analysis), 22/26 (85%) subjects had confirmed Control treatment area closure compared with 24/26 (92%) subjects with

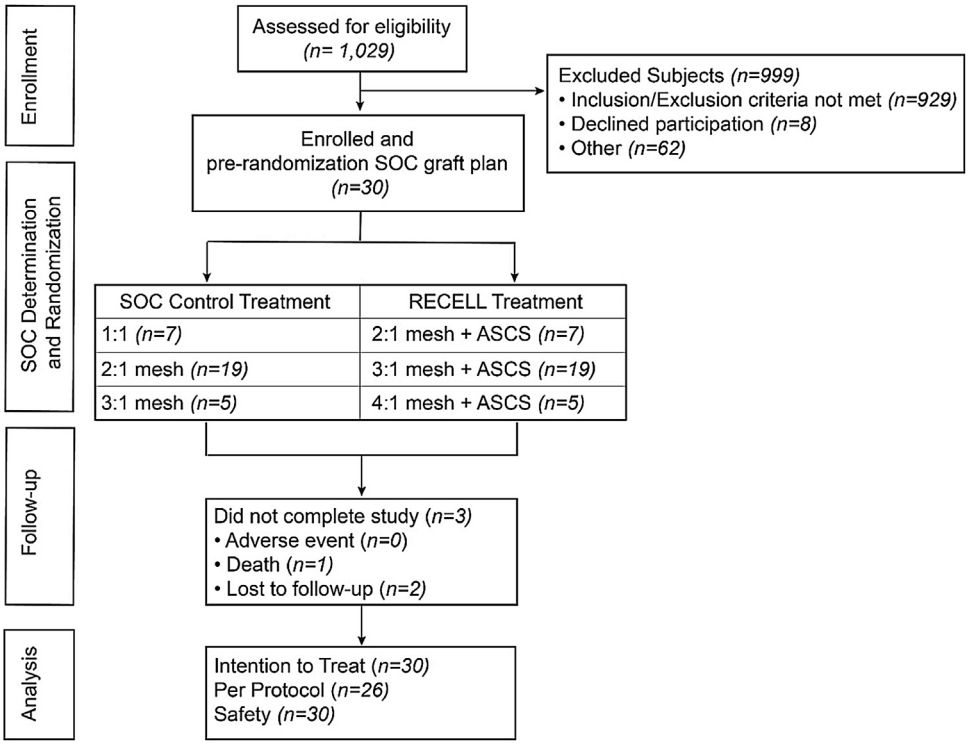

Fig. 1 – CONSORT diagram. Thirty consenting subjects meeting inclusion and exclusion criteria were enrolled into the study. Following burn excision, a STSG plan was developed based on the surgeon's SOC treatment paradigm. Study treatment areas were identified, photo-documented, and randomized to receive either SOC Control treatment (meshed STSG) or RECELL treatment (more widely meshed STSG+ASCS). One subject received STSGs with multiple meshing ratios for both Control and RECELL treatment areas. Additionally, 1 subject was excluded from the PP population for a major protocol deviation. Following treatment, subjects were followed over a 52-week period, and analyses were performed on the ITT, PP, or safety populations, depending on specific effectiveness or safety endpoints.

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Table 2 – Burn injury characteristics.

Safety population (N=30)	
Primary mechanism of burn	
Fire/flames	73.3%
Hot water/steam	13.3%
Other	13.3%
Total estimated burn injury size (%)	
Mean±stdev	21.0%±13.0%
(Range)	5.0%–46.0%
Total estimated area undergoing grafting (cm^2)	
Mean±stdev	2443.0±1675.0
(Range)	600.0–8036.0
Study areas grafted (cm^2)	
Control	
Mean±stdev	528.3±312.5
(Range)	300.0–1960.0
RECELL	
Mean±stdev	554.9±378.3
(Range)	300.0–1605.0

confirmed RECELL treatment area closure. The difference in percentages (Control minus RECELL) was −7.7% with the upper bound of the 97.5% CI (6.40%) within the pre-defined non-inferiority margin (10%), thus establishing the non-inferiority of RECELL treatment (Fig. 2).

3.2. *Relative reduction in donor skin*

Control and RECELL treatment areas were comparable in terms of anatomic location and size. Within the ITT population, mean Control treatment area was 528±312 cm^2 compared with mean RECELL treatment area of 555±378 cm^2 (p=0.123). However, mean area for the Control donor site was 368±150 cm^2 compared with mean area of the RECELL donor site of 264±119 cm^2. This between-treatment difference (32% reduction in utilised donor skin for RECELL treatment) was statistically significant (p<0.001) (Fig. 3A).

The GMR (treatment area/corresponding donor site area) was 1.35 for Control treatment areas and 1.97 for RECELL treatment areas (ITT population, primary analysis population). The GMR of the expansion ratios (RECELL:Control) was 1.46 (p<0.001), establishing the superiority of RECELL treatment for the relative reduction in donor skin utilisation (Fig. 3B).

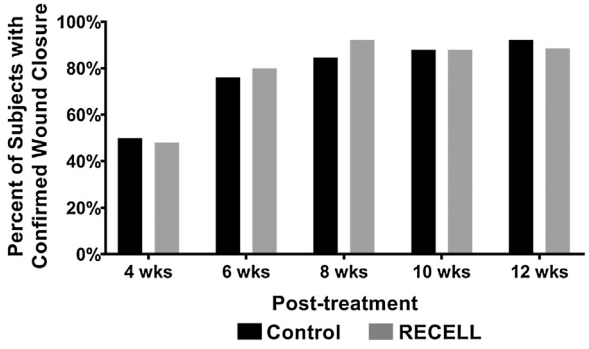

Fig. 2 – Percentage of subjects with confirmed wound closure by treatment areas. Within the Per Protocol (PP) population, the progression of subjects with confirmed wound closure was similar between treatments, with approximately 50% and 80% of subjects achieving 100% re-epithelialization at Week 4 and Week 6, respectively. Wound closure plateaued at approximately 90% at the later visit dates. Non-inferiority of the RECELL treatment for wound closure was tested and established at Week 8 (co-primary endpoint), with the upper limit of the 97.5% CI being 6.40% that is within the pre-defined non-inferiority margin (10%).

3.3. *Subject satisfaction*

Subjects were asked to specify which treatment they were more satisfied with (Area A or Area B). In the ITT population, there was no statistically significant difference (p>0.05) in subject treatment preference at any sampled time point from Week 12 to 52.

3.4. *Patient and Observer Scar Assessment Scale (POSAS)*

The POSAS questionnaire was completed by the subject and by a blinded observer/evaluator at Weeks 12, 24, 36, and 52. No statistically significant differences were observed for the POSAS patient or POSAS observer total scores (Fig. 4A and B, respectively). In addition, no statistically significant differences were observed for the POSAS patient or POSAS observer overall opinions (Fig. 4C and D, respectively). These results indicate no difference in scarring outcome for the 2 treatments, despite using less donor skin for the RECELL treatment.

3.5. *Blinded and non-blinded healing assessments*

Subjects were followed for wound healing by a blinded evaluator and the non-blinded investigator. The extent of healing for each treatment area was captured using the following 5 categories of re-epithelization or closure: 0%, 1%–49%, 50%–79%, 80%–99%, and 100%. No statistically significant difference in treatment area closure was noted for Control versus RECELL in either the ITT population or the PP population based on either blinded or non-blinded assessments at any study visit (p>0.05).

3.6. *Safety*

The same number of subjects (n=17, 57%), though not necessarily the same individuals, experienced AEs at Control and RECELL treatment areas (safety population). Most subjects experienced only mild or moderate AEs (27% and 37% of subjects, respectively). One subject died during the study, with the event attributed to her underlying condition rather than participation in the clinical study. This subject experienced a complicated clinical course following her injury with pneumonia, acute respiratory distress syndrome, and subarachnoid hemorrhage.

No differences were noted in the rate and severity of pre-specified safety events (Table 3), including delayed healing, infection, allergic response to trypsin, wound durability, or

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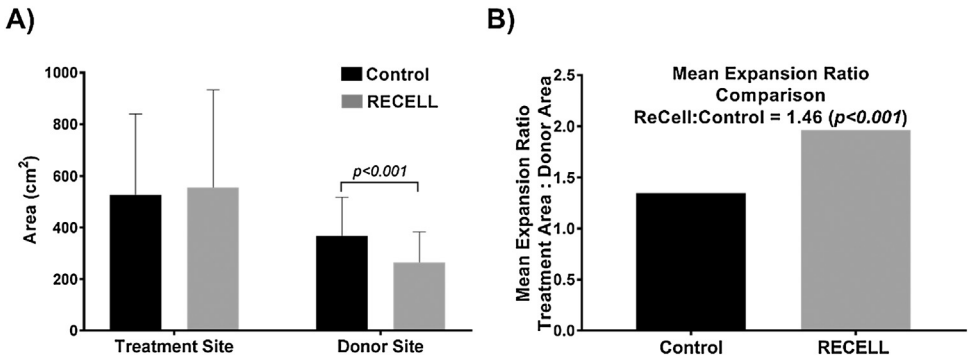

Fig. 3 – Relative reduction in donor skin use.
(A) Within the ITT population, no difference was found in size for the Control and RECELL treatment areas (528 ± 312 cm² and 555 ± 378 cm², respectively). However, a statistically significant decrease in the amount of donor skin to cover the treatment area was observed between the Control and RECELL-treated wounds (368 ± 150 cm² and 264 ± 119 cm², respectively, $p < 0.001$). (B) Within the ITT population, the GMR (treatment area/corresponding donor site area) was 1.35 for the Control treatment and 1.97 for the RECELL treatment. Superiority was established for the relative reduction in donor skin for RECELL treatment compared with Control treatment as the GMR of the expansion ratios (RECELL:Control) was found to be >1 ($p < 0.001$).

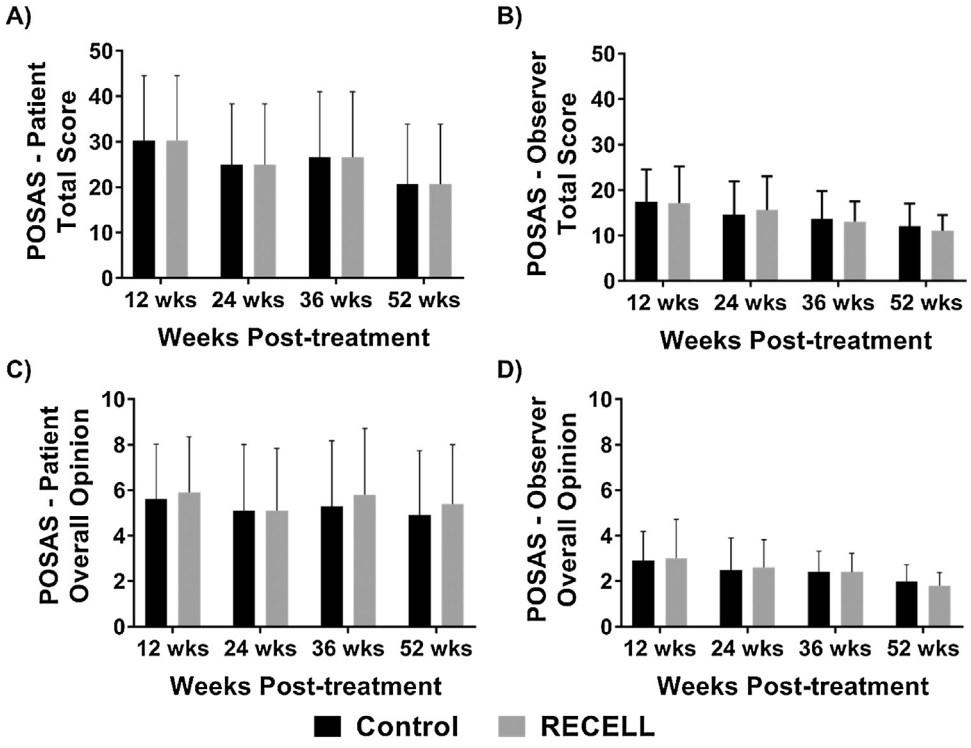

Fig. 4 – Patient and Observer Scar Assessment Scale (POSAS). The POSAS questionnaire was completed by the subject and a blinded observer/evaluator at Weeks 12, 24, 36, and 52. For both the patient and observer scales, individual item scores are summed to produce the total score with higher scores representing worse scars. No statistically significant differences were observed at any time point for any patient or observer scores.

scars necessitating surgical intervention. Pain ratings as assessed using the pain question of the POSAS indicated no difference between RECELL and Control in treatment area pain from Week 1 to Week 12 as well as at Week 52. No statistically significant difference was observed in the incidence of graft loss (surgical intervention required) at the Control and RECELL treatment areas, 16.7% and 13.3%, respectively ($p > 0.05$).

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Table 3 – Key safety outcomes.

Safety population (N=30)		
Pre-specified selected safety events	Control	RECELL
Delayed healing	3 (10.0%)	1 (3.3%)
Infection	2 (6.7%)	0 (0.0%)
Allergic response to trypsin		0 (0.0%)
Wound durability[a]	0 (0.0%)	0 (0.0%)
Scars necessitating surgical intervention[b]	1 (3.3%)	1 (3.3%)

[a] In terms of recurrent wound breakdown following initial complete closure.
[b] Patient also underwent surgical intervention for scar at non-study sites.

3.7. *Representative case example 1 (Fig. 5)*

A 41-year-old white male and smoker sustained a 15% TBSA injury from fire/flames on his lower anterior torso and lower extremities. The study burn wounds were excised and labeled as Area A (left leg) and Area B (torso). Both treatment areas were 600 cm^2 and were randomized to receive Control treatment (1:1 mesh STSG at Area A) or RECELL treatment (2:1 mesh STSG +ASCS at Area B). Donor sites were 570 cm^2 and 420 cm^2 for the Control and RECELL treatments, respectively. At Week 4, the Control treatment area was not healed, but complete re-epithelialization/closure was achieved for the RECELL treatment area. At Week 8, both treatment areas were healed. During the course of the study, neither treatment area underwent re-treatment. At Week 52, comparable scar outcomes were obtained at both treatment areas, as assessed by both the blinded observer and the patient, despite using 26% less donor skin and a more widely meshed STSG for the RECELL treatment.

3.8. *Representative case example 2 (Fig. 6)*

A 68-year-old white female sustained a 20% TBSA injury from hot water/steam on her torso. The study burn wounds were excised and labeled as Area A (320 cm^2 on posterior torso) and Area B (324 cm^2 on left lateral torso). The treatment areas were randomized to receive Control treatment at Area A (3:1 meshed STSG) or RECELL treatment at Area B (4:1 meshed STSG+ASCS). Donor sites were 180 cm^2 and 110 cm^2 for the Control and RECELL treatments, respectively. Complete wound closure was achieved at Week 4 for both treatment areas. At Week 8, both treatment areas remained healed, and during the course of the study, neither treatment area required re-treatment. At Week 52, comparable scar outcomes were obtained at both treatment areas, as assessed by both the blinded observer and the patient, despite using 39% less donor skin and more widely meshed autograft for the RECELL treatment.

4. Discussion

The SOC for treating severe burns is early excision and definitive closure with skin grafting procedures. Studies of this treatment strategy indicate improved survival rates, reduced scarring, shortened hospital length of stay, and reduced infectious complications; however, there are well-known morbidities associated with excision and grafting.

The results from this study establish the safety and effectiveness of the RECELL® System as an autograft-sparing technology indicated for the treatment of burns at the patient's point-of-care via preparation of ASCS applied in combination with meshed STSG for mixed-depth burn injuries, inclusive of full-thickness. Based on the analyses, the study met its co-primary effectiveness endpoints. Non-inferiority was established between Control (SOC meshed STSG) and RECELL (more widely meshed STSG+ASCS) treatments for definitive wound closure by 8 weeks with 85% and 92% of subjects achieving closure for Control and RECELL-treated wounds, respectively. Additionally, RECELL treatment was superior to Control treatment, in that significantly less donor skin (32% reduction, $p<0.001$) was used for the treatment of wounds of similar size. The safety profiles of the 2 treatments were comparable in terms of AEs and selected safety events, with no long-term wound breakdown occurring over the 52-week study period. Furthermore, subjects were equally satisfied with both treatments, and scarring outcomes were similar, despite RECELL treatment using significantly less donor skin.

Meshed autografts have several advantages over sheet autografts including reduction of donor site size, contour, and exudate drainage. However, a major disadvantage in meshing is the surface area within the interstices that must heal by secondary intention, resulting in less than ideal cosmetic outcomes due to contraction. In patients with adequate skin availability, increased mesh ratios are commonly avoided due to this reason and are only used for means of definitive closure in patients with limited donor tissue.

Pre-clinical evidence supports cellular contributions to accelerated epidermal coverage with the addition of a cellular suspension to a widely meshed autograft. Navarro et al., utilized a porcine wound model in which an autologous cellular suspension was applied over a 3:1 meshed split-thickness skin graft and was compared to a 3:1 meshed autograft sprayed with culture medium without cellular suspension. Greater wound re-epithelialization was observed macroscopically in the cellular suspension group on day 5 and day 8 after application, and histological evaluation revealed a more complete confluence, epithelial coverage, and basal cell thickness compared with the control group. Additionally, in wounds sprayed with the cell solution, the dermal-epidermal junction appeared to be more organized compared to the dermal-epidermal junction found in wounds sprayed with culture medium alone [17].

RECELL offers a unique epidermal regeneration strategy, with several advantages over other currently available autologous cell-based methods aimed at achieving definitive closure following excision of a burn [18,19]. As the RECELL® System is used at the patient's point-of-care, ASCS is prepared during the operation, without any requirement for the cell culturing needed for cultured epithelial autografts that takes 2–3 weeks following biopsy. This time difference is critical, as timely wound closure following early excision is essential to

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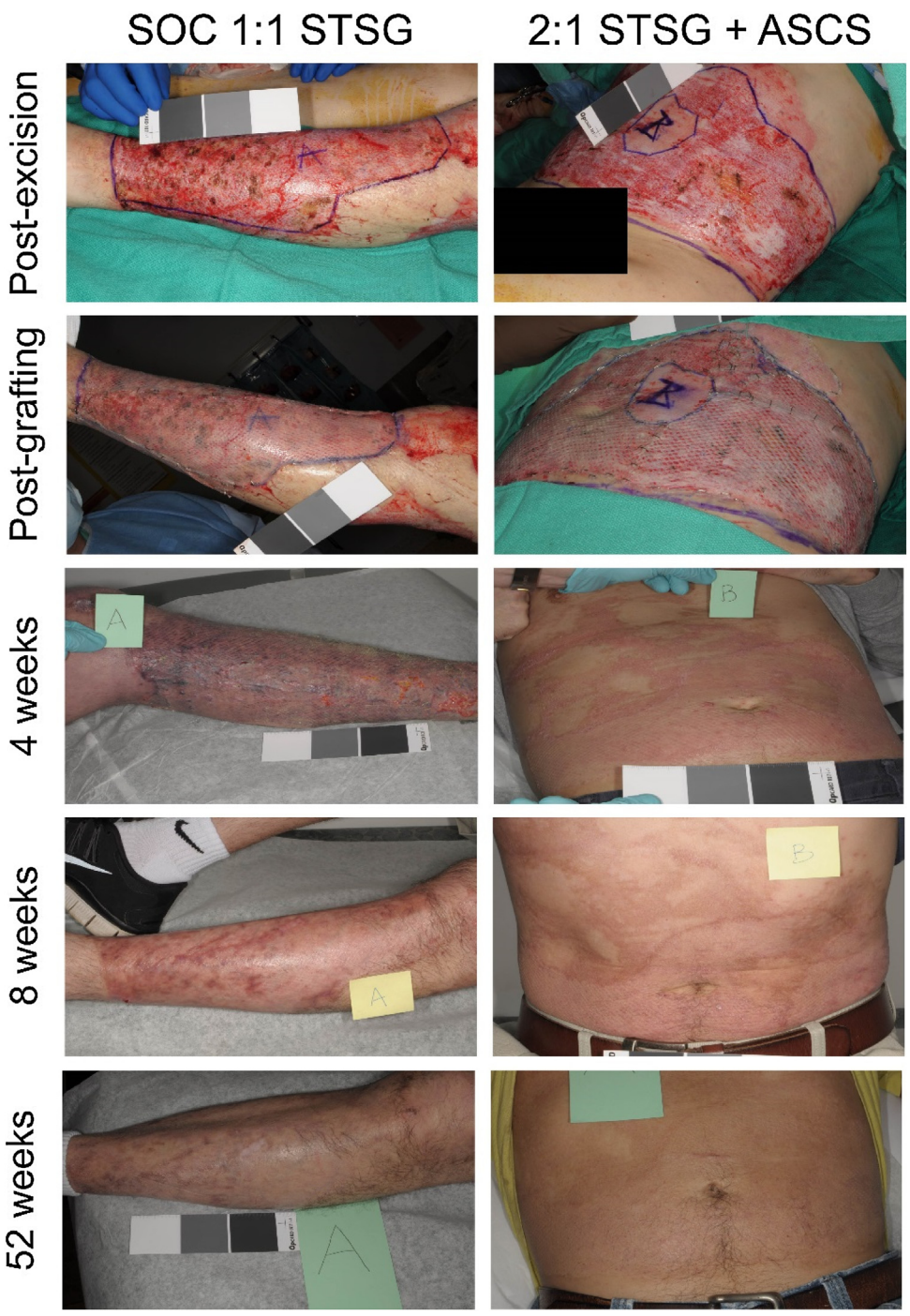

Fig. 5 – Case example 1.
15% TBSA flame burn to the anterior torso and lower legs. The left leg randomized to receive Control treatment (SOC 1:1 meshed STSG, Area A), while the lower anterior torso randomized to RECELL treatment (2:1 meshed STSG+ASCS, Area B). Complete healing was achieved at Week 4 for RECELL treatment (Area B). At Week 8, both treatment areas were healed. At Week 52, a comparable scar outcome was obtained at the 2 areas, despite using 26% less donor skin and a more widely meshed graft for the area that received RECELL treatment.

avoid the formation of hypertrophic scars. Prompt restoration of the epidermis also has been found to increase survival rates, decrease pain and infectious complications, and to reduce the overall hospital length of stay and treatment costs. Additionally, with the use of RECELL, costs associated with cell culturing are avoided, thus substantially reducing the total cost of care. Furthermore, there is a short window for treatment with cultured epithelial autografts, as they can be maintained only for a short period of time outside of the laboratory setting.

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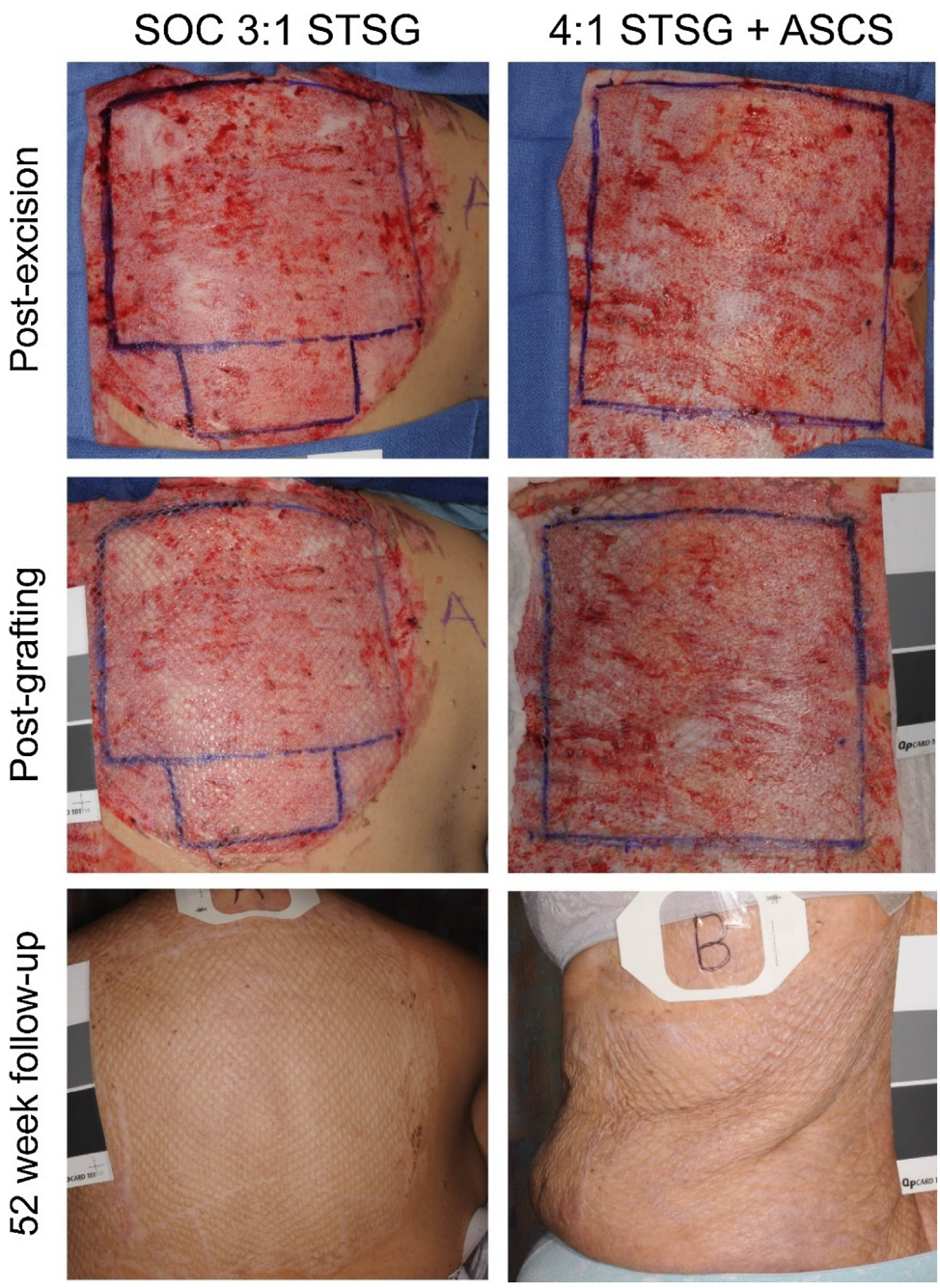

Fig. 6 – Case example 2.
20% TBSA scald burn to the torso. The posterior torso randomized to receive Control treatment (SOC 3:1 meshed STSG, Area A), while the left lateral torso randomized to RECELL treatment (4:1 meshed STSG+ASCS, Area B). Complete wound closure was achieved at Week 4 for both treatment areas. At Week 52, a comparable scar outcome was obtained at the 2 areas, despite using 39% less donor skin and a more widely meshed graft for the area that received RECELL treatment.

The recently published study evaluating RECELL treatment of DPT thermal burns [16] demonstrated that ASCS prepared using the RECELL® System is a viable alternative to STSG for the treatment of burns. The current study extends these findings by demonstrating the benefits of RECELL treatment for more severe burns, both in size and depth of injury. For purposes of comparability and to limit variability between the Control conditions and treatment regimens, both studies excluded burns on joints, hands, feet, and faces; however previously published studies using RECELL demonstrate successful use in injuries across all anatomic locations [7,20-22]. Based on the collective data, the authors conclude that RECELL treatment is comparable to standard autografting for the treatment of deep-partial thickness and full-thickness thermal burns. When one considers that RECELL treatment uses less donor skin to close a given burn, relative to standard autografting,

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with equivalent long-term outcomes, the superiority of RECELL is manifest irrespective of severity, anatomic location, or type of burn.

5. Conclusion

Overall, the results demonstrate the use of ASCS prepared using RECELL, in combination with a widely meshed STSG, successfully achieves definitive wound closure comparable to that achieved with standard autografting, while using significantly less donor skin. Furthermore, this result is achieved with acceptable long-term scar and satisfaction outcomes with no safety concerns. RECELL treatment represents a new strategy for the treatment of burns and addresses an unmet need by overcoming challenges with autografting procedures, including donor site morbidity and availability, as well as limitations surrounding cultured cellular therapies.

Declaration of interests

Dr. Holmes, or his immediate family, have equity interest in the following companies:

1. PermeaDerm, Inc
2. Abbott Labs
3. AbbVie
4. McKesson

Dr. Holmes also serves as a consultant for the following entities:

1. AVITA Medical
2. Stratatech Corp.

Acknowledgements

BARDA Contract No. HHSO100201500028C.

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