Official Title: A Phase 1/2a, Controlled, Randomized, Multicenter Study Evaluating the Efficacy, Safety, and Tolerability of StrataGraft Overlay of Meshed Autograft (SOMA) in Treatment of Full-Thickness Thermal Burns

NCT Number: NCT04765202

Document Date: Protocol Amendment 5: 28 September 2023

STRATAGRAFT® CONSTRUCT

Protocol Title: A Phase 1/2a, Controlled, Randomized, Multicenter Study Evaluating the Efficacy, Safety, and Tolerability of StrataGraft Overlay of Meshed Autograft (SOMA) in Treatment of Full-Thickness Thermal Burns

Protocol Number: MNK01062117

Amendment Number: 5

Compound Number: N/A

Short Title: StrataSOMA

Dosage Formulation: StrataGraft is a living, bioengineered cellular tissue construct that is grown in a rectangular 100 square centimeter format.

Sponsor Name and Legal Registered Address:

Stratatech Corporation, a Mallinckrodt Company
510 Charmany Drive, Suite 150
Madison, WI 53719
United States of America

Regulatory Agency Identifying Number: 010,113

Approval Date: 28 September 2023

SPONSOR SIGNATURE PAGE

My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR) (where applicable), all applicable national and local regulations, protections for privacy, and generally accepted ethical principles for human research such as the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

Refer to e-signature page

Sponsor Signature

[redacted]

ACKNOWLEDGEMENT OF RECEIPT AND UNDERSTANDING OF SPONSOR STUDY MATERIALS

My signature confirms that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR), protections for privacy, and generally accepted ethical principles such as the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

I confirm that I have received, read, and understood the following document(s) for:

PRODUCT:

StrataGraft®

STUDY:

StrataSOMA - Protocol MNK01062117

Protocol Amendment 5, dated 28 September 2023

PRINCIPAL/COORDINATING INVESTIGATOR(S)

Name:

Title:

SIGNATURE_____DATE: _____

SUMMARY OF CHANGES FOR AMENDMENTS

Amendment 5 includes changes related to the FDA's revision of the xenotransplantation requirements for StrataGraft and minor administrative clarifications. A complete summary of the changes reflected in this protocol is provided in Appendix 7.

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1. SYNOPSIS

Protocol Title: A Phase 1/2a, Controlled, Randomized, Multicenter Study Evaluating the Efficacy, Safety, Tolerability of StrataGraft Overlay of Meshed Autograft (SOMA) in Treatment of Full-Thickness Thermal Burns

Short Title: StrataSOMA

Rationale:

The current standard of care for closure of full-thickness (FT) burns is autografting, ie, the surgical harvest of healthy skin from an uninjured site and transplantation of the harvested donor tissue to the burn wound following surgical excision of nonviable tissue. While this method is effective in achieving closure of the original wound, availability of sites for the harvest of donor skin may be limited by burn area and depth, and closure of large areas of injury may necessitate sequential re-harvest of available donor sites. Reduction in the amount of donor tissue necessary to achieve complete wound closure is of clinical benefit, as the harvest of a donor site creates an additional partial-thickness wound which adds to the patient's overall wound burden and is itself painful, susceptible to infection and scarring, and can convert to a FT wound. As a result, there is an urgent need for alternatives that reduce the area of donor site needed to achieve closure of burn wounds. The described investigational treatment is anticipated to permit the use of more widely-meshed autograft than the comparator autograft treatment, thereby reducing the total area of donor skin needed to achieve wound closure.

Objectives and Endpoints

The overall objective of this study is to evaluate the efficacy, safety, and tolerability of StrataGraft when used as an overlay of meshed autograft to facilitate wound closure and reduce donor site harvest in the treatment of FT thermal burns.

In this protocol, the 2 comparative study treatment sites are referred to as follows:

1. The study treatment that is **S**trataGraft **O**verlay of **M**eshed **A**utograft (SOMA), where meshed autograft is applied to the burn area and covered with StrataGraft, hereafter is referred to as "SOMA Tx."
2. The control treatment that is meshed autograft alone as applied to a burn area; hereafter is called "AG Tx."

When collectively referring to both study treatments (ie, the SOMA Tx and the control AG Tx), they are hereafter referred to as "Study Tx."

Efficacy

Objectives	Endpoints
Primary	**Co-Primary Endpoints**
Evaluate the efficacy of SOMA Tx	• Calculated percent reduction of donor skin (as defined by [1-(AG Tx mesh ratio/SOMA Tx mesh ratio) × 100]) at Month 2 • Difference in percent of SOMA Tx sites and AG Tx sites with confirmed complete wound closure without additional autografting at Month 2
Secondary	
Evaluate the efficacy of SOMA Tx	• Incidence of confirmed complete wound closure of the Study Tx sites at Days 14, 21, 28, and 42, and Month 2 and Month 3 • Percent re-epithelialization of the Study Tx sites at Day 14, 21, 28, and 42, and Month 2 and Month 3 • Percent subjects with durable wound closure of Study Tx sites at Months 3, 6, and 12 • Patient and Observer Scar Assessment Scale (POSAS)/ Patient Scar Assessment Questionnaire (PSAQ) scores of Study Tx sites at Day 28, Months 2, 3, 6, and 12
Tertiary/Exploratory	
Health Care Resource Utilization (HCRU)	• Location of care for StrataGraft application (eg, inpatient hospital, outpatient/ambulatory hospital, clinic) • Treatments used for all other non-study burn areas following excision and % total body surface area (TBSA) treated with each • Number and duration of operating room procedures required for study burn treatment • Length of hospital stay • Prescription drugs given for pain control • Antibiotics given for outpatient use at discharge • Re-admission within 30 days after discharge • Whether a re-admission is planned

	• Length of hospital stay after re-admission
Exploratory	
	• Calculated total area of autologous (donor) skin applied to Study Tx sites by Month 6 • Effect of total wound burden on rate of wound closure

Safety

Objectives	Outcome Assessments
Evaluate the safety of SOMA Tx	• Incidence of treatment-emergent adverse events (TEAEs) throughout study • Incidence of TEAEs related to each of the Study Txs • Incidence of wound infection-related events at Study Tx sites • Clinically significant changes in vital signs throughout study compared to Baseline • Clinically significant changes in laboratory values between Baseline and Day 28 • Clinically significant changes in panel reactive antibodies (PRA) and anti-bovine serum albumin (BSA) levels between Baseline and Month 3 • Concomitant medication use

Outcome Measures

Primary Outcome Measures

Number of treatment sites with complete wound closure without additional autografting at Month 2

Number of subjects with durable wound closure of the study treatment sites without additional autografting at Month 12

Overall Design:

This is a Phase 1/2a, multicenter, open-label, randomized, within-patient controlled study in subjects with 2% to 49% (inclusive) TBSA thermal burn. The overall objective of this study is to evaluate the efficacy, safety, and tolerability of StrataGraft as an overlay for meshed autograft to promote wound closure and reduce donor site areas harvested in the treatment of FT thermal burns.

The targeted enrollment for this study is 40 subjects with FT thermal injury. On each subject, 2 wounds, comparable in area, wound bed composition (fat, fascia, or muscle), and kinesiologic stressors will be identified, designated as Sites A and B, and randomized to receive either AG Tx (control) or SOMA Tx, such that each subject receives both treatments. Following excision, the control autograft treatment site will receive meshed split-thickness skin graft, while the SOMA treatment site will receive autograft that is meshed at 1 or 2 mesh ratio(s) greater than the control treatment site and overlaid with StrataGraft meshed up to 1:1.

Cohort 1 will consist of 20 subjects randomized to one of 2 groups: Group 1 (n=10) will receive AG Tx consisting of autograft alone (mesh ratio "m", per clinical judgment) compared to SOMA Tx in which m+1:1 meshed autograft is overlaid with StrataGraft, while Group 2 (n=10) will receive AG Tx with autograft (mesh ratio "m" per clinical judgment) compared to SOMA Tx in which m+2:1 meshed autograft is overlaid with StrataGraft, applied to wounds of 100 to 400 cm^2 in area. Subjects will be followed and assessments performed per the Schedule of Activities (Table 1). Each subject will be determined to be a success or failure based upon the criteria below, and one of the 2 treatments, m+1 or m+2, will be determined to meet the *a priori* established criteria within the algorithm to move forward:

- Percent closed (re-epithelialization) at Day 28, with success declared if the difference between paired wounds $\leq$ 10%
- Total score of Observer assessment of the POSAS at Day 28, with success declared if the difference between paired wounds $\leq$ 20%

Cohort 2 will consist of 20 subjects, all of whom will receive the SOMA Tx (with autograft meshed at m+1 or m+2) identified following assessment of Cohort 1 and the AG Tx control, applied to wounds of 400 to 1,900 cm^2 in area. Subjects will be followed and assessments performed per the Schedule of Activities.

Number of Participants:
A maximum of 40 participants will receive study treatment.

Treatment Groups and Duration:

This study is open-label. Subjects will serve as their own control. Subjects will be randomized to receive autograft, meshed at a ratio per clinician judgment at 1 treatment site (m), and StrataGraft overlay of autograft at either m+1 or m+2, relative to the control mesh ratio.

It is anticipated that each subject will participate in this study for up to 14 months: up to 2 weeks of screening followed by up to 12 months (± 4 weeks) of post-treatment observation.

ESTIMATED DURATION OF STUDY

Enrollment ~36 months

Duration of subject participation up to 60 weeks

Total study duration ~96 months

2. SCHEDULE OF ACTIVITIES

Table 1: Schedule of Activities

Assessments	Day -14 to Day -1	Day 1	Day7± 1d	Day 14± 2d	Day 21 ± 2d	Day 28± 3d	Day 42± 4d	Month 2 ± 4d	Month 3 ± 7d	Month 6 ± 2Wks	Month 12± 4Wks
Informed consent[a]	√										
Physical examination and medical history review	√										
Laboratory tests (CMP and CBC with differential)[b]		√				√					
Pregnancy test (women of childbearing potential)[b]	√										
Blood samples for immunogenicity (PRA & anti-BSA)[c]		√							√		
Vital signs	√	√	√	√	√	√	√	√	√	√	√
Archival blood sample collection[c]		√									
Study Tx application		√									
Photograph Study Tx sites[d]		√	√	√	√	√	√	√	√	√	√
Study site surveillance[e]		√	√	√	√	√	√	√	√	√	√
Blinded wound assessments[f]			√	√	√	√	√	√	√	√	√
Concomitant medications		√	√	√	√	√	√	√	√	√	√
Concomitant procedures		√	√	√	√	√	√	√	√	√	√
Assessment and reporting of AEs	√	√	√	√	√	√	√	√	√	√	√

Assessments	Day -14 to Day -1	Day 1	Day7± 1d	Day 14± 2d	Day 21 ± 2d	Day 28± 3d	Day 42± 4d	Month 2 ± 4d	Month 3 ± 7d	Month 6 ± 2Wks	Month 12± 4Wks
Quality of healed Study Tx sites (POSAS/PSAQ)[g]						√		√	√	√	√
Biopsy of healed SOMA Tx site and adjacent uninjured skin[h]									√		

[a] Study Tx consent, including consent for photos, biopsy and for direct contact by sponsor post-study.
[b] Processed by local laboratory. Obtain within 48 hours prior to application of StrataGraft.
[c] Processed by central laboratory. Collected BEFORE StrataGraft placement.
[d] Photos will be taken of the Study Tx sites prior to excision, following excision and hemostasis, and following placement of the Study Txs. During hospital stay, photos will be taken weekly. Following hospital discharge, the subject will have the option to submit photographs of the Study Tx sites each week until Month 3, every other week until Month 6, and then monthly until the Month 12 visit.
[e] Study site surveillance includes assessment of local wound area for signs of infection, site adverse events, and graft loss.
[f] Blinded assessor will assess all treatment sites for percent epithelialization beginning at Day 7 then and daily, or as often as possible, during dressing changes until complete closure is observed. A second observation of complete closure at least 2 weeks after the initial observation is required to confirm closure. Thereafter maintenance of closure will be assessed at each study visit, to assess durability of closure.
[g] All POSAS Observer assessments will be performed by blinded assessor, first at the time of closure, and at Day 28, Months 2, 3, 6 and 12.
[h] Biopsies will be collected from subjects in Cohort 1 and processed by the central laboratory.

CMP = complete metabolic panel; CBC = complete blood count; PRA = panel reactive antibodies; anti-BSA = anti-bovine serum albumin; Study Tx = study treatment; AE = adverse event; POSAS = Patient and Observer Assessment Scale; PSAQ = Patient Scar Assessment Questionnaire; SOMA Tx = StrataGraft Overlay of Meshed Autograft treatment

3. INTRODUCTION

In the United States in 2013, 53,220 patients required hospitalization for severe skin loss due to burn-related incidences and, of those individuals, 29.4% (15,625) required the surgical intervention of skin grafting (McDermott, 2016). Depending upon the extent of the injury, hospitalization can often be protracted. For survivors, the average length of stay was slightly greater than 1 day per percent total body surface area (TBSA) burned based on the 2018 National Burn Repository annual report of data collected from 101 health care facilities between January 2008 and June 2017 (American Burn, 2017). The mean length of hospital stay is close to double (8.1 vs 4.5 days) that of any other diagnosis requiring hospital stay. A higher percentage of people with burn-related hospital inpatient stays die from their burn-related injuries (2.2% of 53,220 total burned inpatients) compared to all other diagnosis requiring hospital inpatient stays (1.9% of 35,544,572 total inpatients) (McDermott, 2016).

After stabilization of the critical care issues in those who sustain a burn-injury, attention is directed toward burn wound management. The ultimate aim of burn wound management is to prevent wound infections and facilitate closure of the wounds, either spontaneously or by autologous skin grafts. Key elements of burn wound management include cleansing, debridement and/or surgical excision, and application of topical antimicrobial agents and dressings.

Regardless of the age of the patient, evidence suggests that early excision of burn eschar is effective in decreasing morbidity, improving the mortality rate, and reducing length of stay (Herndon, 1989; Muller, 1994) as well as hospital costs (Munster, 1994). Excised areas are usually closed with autograft, or if not available, allograft, xenograft, or other skin substitute is used until autograft is available or the wound spontaneously closes. Availability of autologous donor tissue, however, is limited by the extent of the burn injury, and in larger injuries, donor sites are often repeatedly harvested, increasing the likelihood of scarring at those sites. As such, methods to reduce the amount of donor tissue needed to achieve wound closure are always sought.

3.1. Study Rationale

StrataGraft is under development by Stratatech, a Mallinckrodt Company, as an alternative to autografting to promote the healing of thermal burns.

Clinical data in adults have suggested that treatment of deep partial-thickness (DPT) thermal burns with StrataGraft can result in wound closure while reducing or eliminating the need for autograft (Holmes, 2019). Clinical data have also shown that this tissue construct does not transplant but is replaced by the patient's cells as the wound heals. StrataGraft is an allogeneic human tissue-engineered product and not an autologous, patient-specific product.

This study is being conducted in order to evaluate safety and clinical outcomes associated with the use of StrataGraft as an overlay to meshed autograft to promote wound closure and reduced area of donor site harvest in the treatment of full-thickness (FT) thermal burns in a population of subjects with thermally-induced FT burns.

This study will be conducted in compliance with applicable regulations and guidance related to Good Clinical Practice (GCP) and this protocol.

3.2. Background

StrataGraft (Stratatech, a Mallinckrodt company, Madison, WI) is an allogeneic, cellularized scaffold construct currently under evaluation for the treatment of patients with FT and DPT burns. It is bilayer, with both an epidermis and a dermis. The epidermal layer is composed of viable, stratified, human keratinocytes on a dermal layer of human fibroblasts embedded in an animal-derived, non-bovine sourced Type I collagen. The epidermal layer of StrataGraft is composed of NIKS® keratinocytes, a consistent source of neonatal human epidermal progenitor cells (Allen-Hoffmann, 2000). In preclinical studies, NIKS keratinocytes exhibit characteristic epidermal differentiation, including the development of a basal cell layer with adhesion proteins and hemi-desmosomes that attach to the dermal equivalent (Allen-Hoffmann, 2000). StrataGraft reproduces the structural and biological properties of both the epidermal and dermal components of interfollicular skin. In addition, it exhibits good intraoperative handling characteristics and can be meshed and secured to the wound bed by surgical stapling, suturing, or gluing.

StrataGraft has been evaluated in the treatment of DPT wounds in the completed studies STRATA2011 and STRATA2016.

In the STRATA2011 phase 1b study of 30 subjects, none of the wounds treated with StrataGraft underwent autografting prior to Day 28 and 93% of the wounds exhibited complete wound closure at Week 12 (Holmes, 2019). Results from the STRATA2011 clinical study supported evidence that treatment of complex skin defects containing intact dermal elements with StrataGraft promotes skin re-epithelization at the burn site without the need for surgical harvesting and transplantation of an autograft.

In the STRATA2016 phase 3 study of 71 subjects, an analysis of the co-primary endpoints of the average percent area of StrataGraft treatment autografted by Month 3 and the percent durable wound closure without additional autografting was performed. The study outcomes met both co-primary endpoints with a statistically significant decrease in mean percent area autografted sites when comparing StrataGraft treatment sites to the autografted sites (control) ($p < 0.0001$). By Month 3, 3 subjects (4.2%) required autografting of the StrataGraft treatment site, two of whom also required additional autografting of their autografted study treatment site. Additionally, success for StrataGraft durable wound closure was observed when the resultant 95% confidence interval (CI) lower bound of 74.4% of subjects for StrataGraft was greater than the predetermined success of the 95% CI lower bound of ≥ 50% of subjects, when compared with autograft. The resulting percent durable wound closure was similar in both treatment groups (StrataGraft 83% vs autograft 86%).

These studies in adults with DPT thermal burns have demonstrated that, in the majority of cases, StrataGraft treatment can substantially reduce or eliminate the need for autograft to achieve wound closure.

Additionally, StrataGraft has been evaluated in the treatment of FT wounds in 2 previously completed studies: STRATA2001 and STRATA2014.

The STRATA2001 study investigated the administration of StrataGraft in 15 subjects with FT complex skin defects (Centanni, 2011). In this study, surgically debrided acute wounds were divided into half and each half randomized to receive either cadaver skin or StrataGraft as temporary closure prior to definitive autografting. The area of treatment was escalated in each of 3 cohorts, increasing from application of 44 to 220 cm^2 of StrataGraft. At a second planned procedure, about 2 weeks after placement, the StrataGraft and cadaver skin were removed and, if the wound was judged ready, autograft was applied. At Week 2 after StrataGraft placement, autograft "take" was comparable between cadaver skin and StrataGraft for all 3 cohorts combined (97.7% vs 96.7% for StrataGraft and cadaver skin, respectively) (Schurr, 2009). Further, StrataGraft demonstrated a safety profile comparable to cadaver allograft.

The STRATA2014 study was designed to assess the safety and efficacy of single or repeated applications of StrataGraft in replacing autograft for the closure of FT skin defects. In this study, up to 20 subjects were to be enrolled into 2 cohorts with 10% to 49% (inclusive) TBSA skin loss and containing an FT component. Though no safety concerns were noted in data safety monitoring board review of multiple applications of StrataGraft treatment per subject, the study was closed after enrollment of 3 subjects. All 3 subjects required autografting of some portion of the StrataGraft treatment site (wound areas 165 cm^2 to 180 cm^2). Because of the small sample size, there was insufficient evidence to draw conclusions for study efficacy assessments.

For StrataGraft treatment of FT skin defects, the STRATA2001 results demonstrated outcomes of StrataGraft application to an excised FT wound bed to be similar to those achieved with cadaveric allograft, with subsequent autograft take to be greater than 95%. This study, StrataSOMA, will evaluate the efficacy, safety, and tolerability of StrataGraft to promote durable closure of burn wounds following application on top of meshed and expanded autograft, while reducing the area of donor site harvested in the treatment of FT thermal burns.

3.3. Benefit/Risk Assessment

Results to date indicate that StrataGraft is well tolerated and no clinically observable allogeneic immune responses have been reported. The most common noted adverse reaction associated with StrataGraft treatment is pruritus.

Theoretical risks specific to StrataGraft treatment include development of an immune response to the allogeneic cells of StrataGraft and the need for subsequent autografting of the StrataGraft treatment site. Because StrataGraft contains human cells, there is the possibility of transmission of an infectious agent. Additionally, StrataGraft contains glycerin, therefore in patients who have a glycerin sensitivity, there is a risk of an allergic reaction.

While no clinically relevant immune response to StrataGraft has been seen in STRATA2001, STRATA2011, STRATA2014, or STRATA2016, or there is a theoretical possibility that subjects who mount an immune response to the allogeneic cells of StrataGraft and who then become candidates for receiving solid organ transplants could experience a narrowing of the suitable donor pool.

Data from STRATA2001 showed that autograft take after treatment of the wound bed with StrataGraft was similar to cadaver allograft, 97% and 96%, respectively. Additionally, the 2 STRATA2011, the 3 STRATA2014, and the 3 STRATA2016 subjects who received autograft at

sites previously treated with StrataGraft showed complete wound closure before or at Month 3, demonstrating that treatment with StrataGraft does not impede achievement of wound closure in the event autograft is used to achieve definitive closure.

StrataGraft is a xenotransplantation product because in the past, one of the cell types used to make StrataGraft was grown with mouse cells. The cell banks have been tested and found to be free of detectable infectious agents and mouse cells are no longer used in the manufacture of StrataGraft. There have been no identified health concerns associated with these mouse cells.

Recipients of xenotransplantation products are generally not eligible, per federal regulations, to donate whole blood, blood components, source plasma or source leukocytes. However, individual blood banks may request an exception from FDA. StrataGraft recipients wishing to donate blood or blood products should check with their donation center. StrataGraft recipients who otherwise meet the donor requirements are eligible to donate human cells, tissues, breast milk, ova, sperm, or body parts for transplantation.

The benefit of treating burns with StrataGraft is that the viable cells of StrataGraft produce and secrete a variety of peptides, growth factors, and cytokines that are collectively anticipated to facilitate wound repair and tissue regeneration. Clinical data suggest that treatment of DPT thermal burns with StrataGraft can result in wound closure while reducing or eliminating the need for autograft and also suggest that the construct does not transplant, but is replaced by the subject's cells as the wound heals (Holmes, 2019). The anticipated benefit of StrataGraft treatment as an overlay of meshed autograft is reduction in autograft donor site harvest; this treatment is anticipated to close the open wound areas (interstices) left after treatment with meshed and expanded autograft, providing clinicians the ability to use more widely expanded autograft (ie, with a higher mesh ratio), thereby reducing the area of autograft harvest from donor sites.

More detailed information about the known and expected benefits, risks, and reasonably expected adverse events (AE) can be found in the Investigator's Brochure.

4. OBJECTIVES AND ENDPOINTS

The overall objective of this study is to evaluate the efficacy, safety, and tolerability of StrataGraft when used as an overlay of meshed autograft to facilitate wound closure and reduce donor site harvest in the treatment of FT thermal burns.

In this protocol, refer to the 2 comparative study treatment sites as follows:

1. The study treatment is **S**trataGraft **O**verlay of **M**eshed **A**utograft (SOMA), where meshed autograft is applied to the burn area and covered with StrataGraft, hereafter will be referred to as "SOMA Tx."
2. The control treatment is meshed autograft alone as applied to a burn area; hereafter is called "AG Tx."

When collectively referring to both study treatments (ie, the SOMA Tx and the comparator AG Tx), hereafter refer to "Study Tx."

Efficacy

Objectives	**Endpoints**
Co-Primary	
Evaluate the efficacy of SOMA Tx	• Calculated percent reduction of donor skin (as defined by [1-(AG Tx mesh ratio/SOMA Tx mesh ratio) × 100]) at Month 2 • Difference in percent of SOMA Tx sites and AG Tx sites with confirmed complete wound closure without additional autografting at Month 2
Secondary	
Evaluate the efficacy of SOMA Tx	• Incidence of confirmed complete wound closure of the Study Tx sites at Days 14, 21, 28, and 42, Month 2 and Month 3 • Percent re-epithelialization of the Study Tx sites at Day 14, 21, 28, and 42, Month 2 and Month 3 • Percent subjects with durable wound closure of Study Tx sites at Months 3, 6, and 12 • Patient and Observer Scar Assessment Scale/Patient Scar Assessment Questionnaire (POSAS/PSAQ scores of Study Tx sites at Day 28, and Months 2, 3, 6, and 12

Tertiary/Exploratory	
Health Care Resource Utilization (HCRU)	• Location of care for StrataGraft application (eg, inpatient hospital, outpatient/ambulatory hospital, clinic) • Treatments used for all other burn areas following excision and % TBSA treated with each (ie, other than Study Tx sites) • Number and duration of operating room procedures required for study burn treatment • Length of hospital stay • Prescription drugs given for pain control • Antibiotics given for outpatient use at discharge • Re-admission within 30 days after discharge • Whether a re-admission is planned • Length of hospital stay of re-admission
Exploratory	• Calculated total autologous (donor) skin applied to Study Tx sites by Month 6 • Effect of total wound burden on rate of wound closure

Safety

Objectives	Outcome Assessments
Evaluate the safety of SOMA Tx	• Incidence of treatment-emergent AEs (TEAEs) throughout study • Incidence of TEAEs related to each of the Study Txs • Incidence of wound infection-related events at Study Tx sites • Clinically significant changes in vital signs throughout study compared to Baseline • Clinically significant changes in laboratory values between Baseline and Day 28

	• Clinically significant changes in panel reactive antibodies (PRA) and anti-BSA levels between Baseline and Month 3 • Concomitant medication use

Outcome Measures:

Number of treatment sites with complete wound closure without additional autografting at Month 2.

Number of subjects with durable wound closure of the study treatment sites without additional autografting at Month 12.

5. STUDY DESIGN

5.1. Overall Design

This is a multicenter, open-label, randomized, within-patient, controlled, mesh-ratio-finding study in subjects with 2% to 49% (inclusive) TBSA thermal burn. The objective of this study is to evaluate the efficacy, safety, and tolerability of StrataGraft as an overlay for meshed autograft to promote complete wound closure (Food and Drug Administration [FDA], 2006) and reduced area of donor site harvested in the treatment of FT thermal burns.

The targeted enrollment for this study is up to 40 subjects with FT thermal injury, each subject receiving both SOMA Tx and AG Tx and serving as his or her own control. Subjects will be enrolled into one of 2 cohorts, the first Cohort to determine a mesh ratio escalation when autograft is used in conjunction with StrataGraft, and the second Cohort to assess the endpoint variability. Biopsies of the healed StrataGraft-treated wound and adjacent uninjured skin will be obtained from subjects in Cohort 1 at Month 3 to assess tissue architecture.

5.2. Participant and Study Completion

Approximately 40 participants will be enrolled and randomized in this study. Screening begins with execution of consent and enrollment occurs at the time of placement of StrataGraft.

5.3. End of Study Definition

Subjects enrolled in this study will complete participation after completion of the Month 12 assessments, withdrawal of consent, or Investigator withdrawal.

5.4. Scientific Rationale for Study Design

The current standard of care for closure of FT burns is autografting, ie, the surgical harvest of healthy skin from an uninjured site and subsequent transplantation of the donor tissue to the wound following surgical excision of nonviable tissue from the burn. While this method is effective in achieving closure of the original wound, optimal sites for the harvest of donor skin are often limited, and closure of large areas of injury may necessitate sequential re-harvest of available donor sites. Additionally, the donor site is painful, susceptible to infection and scarring, and can convert to a FT wound. As a result, there is an urgent need for treatment alternatives that reduce donor site harvesting for treatment of severe burns.

5.5. Justification for Dose

A major factor limiting survival following extensive thermal injury is insufficient availability of healthy donor sites to provide enough skin for the required grafting procedures. In order to minimize the amount of donor site harvested, donor skin is often meshed to allow expansion of the autograft and increase the wound area that can be covered. However, such expansion carries risks such as infection of the wound bed within the interstices or long-term scarring of these open areas, resulting impairment of the graft to successfully incorporate and revascularize (ie,"take") into the wound due to desiccation in the former or in a poor cosmetic and/or functional outcome in the case of the latter. Any such graft loss usually necessitates additional grafting and increases

the risks of morbidity and mortality. Alexander hypothesized that the application of allograft over widely meshed autograft would serve as a protective biological dressing as the autograft re-vascularized and then re-epithelialized the mesh interstices. They reported the successful use of cadaver skin as an overlay of widely meshed autograft in preventing these potential adverse outcomes in 14 subjects and 22 grafting procedures of 1% to 15% TBSA. However, although successful in gaining wound closure, it did not prevent scarring in the interstices due to the lack of a dermis in these areas (Alexander, 1981).

The use of Apligraf®, a similar FT living-skin analog, was reported in 38 patients comparing outcomes to an intrapatient control of split thickness skin graft alone meshed at the same ratio (Waymack, 2000). Under the Apligraf overlay, the median number of days to >75% closure of the interstices was 8 days compared to 13 days for the control sites. Of interest, wounds with Apligraf overlay of split thickness skin graft exhibited significant improvement in pliability compared to the autograft alone wounds with the former achieving normal pliability in a median of 35 days compared to such restoration in the autograft alone wounds in a median of more than 849 days. However, Apligraf has not been approved for this use.

5.6. Study Stopping Criteria

In this study, safety will be monitored by the Medical Monitor and Global Safety Lead from the Sponsor, as well as the Data Safety Monitoring Board (DSMB). The DSMB will be independent of study conduct. Subject enrollment will be paused pending discussion with DSMB if any of the following occur:

- Unexpected infection at the StrataGraft treated site that is possibly or probably related to StrataGraft and is an SAE
- Severe acute hypersensitivity reaction attributed to StrataGraft
- Death attributed to StrataGraft

In the event that any of these events occur, the local institutional review board (IRB) and DSMB will be notified. The Medical Monitor will review the safety data associated with the AE with the Investigator and generate a summary narrative. The Medical Monitor, Global Safety Lead, and DSMB will conduct a comprehensive review of the safety data prior to resumption of subject enrollment. The findings from the DSMB will be discussed with the Sponsor clinical team and Clinical Trial Lead prior to any action being taken.

6. STUDY POPULATION

Subjects aged 18 to 75 (inclusive) of either sex with 2% to 49% (inclusive) TBSA thermal burn, including a proportion clinically indicated for surgical excision and autografting.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Subject-specific criteria:

1. Participant must be 18 to 75 years of age (inclusive), at the time of signing the informed consent
2. Male or female
3. 2% to 49% (inclusive) TBSA thermal burn area, including a proportion of FT injury clinically indicated for surgical excision and autografting
4. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

Treatment site-specific criteria:

5. Full thickness, thermal burns for which excision and autografting are clinically indicated. Matching treatment areas of:
   a. 100 to 400 cm^2 each are required for subjects enrolled in Cohort 1
   b. 400 to 1,900 cm^2 each for subjects enrolled in Cohort 2
6. Study Tx sites located on the torso or limbs (may cross joints)

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Subject-specific criteria:

1. Prisoners
2. Burns of chemical or electrical (non-thermal) etiology
3. Pregnant women
4. Subjects receiving systemic immunosuppressive therapy at the time of injury
5. Subjects with a known history of malignancy, excluding extirpated basal or squamous cell carcinoma or melanoma.
6. Pre-admission insulin-dependent diabetic subjects
7. Subjects with concurrent conditions that in the opinion of the investigator may compromise subject safety or study objectives, such as clinically significant inhalation injury or inadequate fluid resuscitation

8. Expected survival of < 3 months
9. Treatment sites on the face, head, neck, hands, feet, buttocks, genitalia, and perineum
10. Treatment sites with exposed bone or tendon
11. Treatment sites directly adjacent to unexcised eschar
12. Clinical determination of infection at the anticipated treatment sites
13. Previous autografting of the treatment sites
14. Concurrent participation in the treatment arm of another interventional agent or within the 30 days prior to enrollment to this study (an "interventional agent" is any drug, device or biologic that is being administered under an IND or IDE. Participation in studies of nutritional supplements is not exclusionary).

6.3. Lifestyle Restrictions

No lifestyle restrictions are imposed.

6.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently treated with StrataGraft.

7. TREATMENTS

This is a Phase 1/2a, multicenter, open-label, randomized, within-patient controlled study in subjects with 2% to 49% (inclusive) TBSA thermal burn. Targeted enrollment for this study is up to 40 subjects with FT thermal injury. On each subject, 2 wounds comparable in area, wound bed composition (fat, fascia, or muscle), and kinesiologic stressors, will be identified, designated as Sites A and B, and randomized to receive either control AG Tx or SOMA Tx, such that each subject receives both treatments. Following excision, the control AG Tx site will receive meshed split-thickness skin graft meshed per clinician judgment while the SOMA Tx site will receive autograft that is meshed at 1 or 2 mesh ratio(s) greater than the control treatment site and overlaid with StrataGraft meshed up to 1:1.

Cohort 1 will consist of up to 20 subjects randomized to one of 2 groups: Group 1 (n=10) will receive autograft (mesh ratio "m", per clinical judgment) compared to m+1:1 meshed autograft overlaid with StrataGraft, while Group 2 (n=10) will receive meshed autograft (mesh ratio "m", per clinical judgment) compared to m+2:1 meshed autograft overlaid with StrataGraft, applied to wounds of 100 to 400 cm^2 in area. Subjects will be followed, and assessments performed per the Schedule of Activities (Table 1). Each subject will be determined to be a success or failure based upon the criteria below, and one of the 2 treatments, m+1 or m+2, will be determined to meet the *a priori* established criteria within the algorithm to move forward.

- % closed (re-epithelialization) at Day 28, with success declared if the difference between paired wounds $\leq$ 10%
- Total score of Observer assessment of the POSAS at Day 28, with success declared if the difference between paired wounds $\leq$ 20%.

Cohort 2 will consist of 20 subjects, all of whom will receive the treatment successfully meeting the criteria in Cohort 1. Briefly, matched paired wounds will be randomized to receive either autograft (mesh ratio "m", per clinical judgment) or meshed autograft 1 or 2 ratios greater than "m" with StrataGraft overlay, to areas of 400 to 1,900 cm^2. Subjects will be followed, and assessments performed per the Schedule of Activities (Table 1).

Additional details may be found in the study's manual of procedures, including guidance on determining the appropriate mesh ratios and the use of systemic and topical antibiotics/antimicrobials.

7.1. Treatments Administered

Study Tx	StrataGraft Construct
Dosage formulation	StrataGraft is a viable and metabolically active allogeneic human NIKS keratinocytes and human dermal fibroblasts cellularized layered scaffold. It is supplied in a rectangular, 100 cm^2 format, loosely adherent to a polycarbonate membrane of a tissue insert. StrataGraft is stored at -70°C to -90°C until thawed for use.
Unit dose strength(s)/Dosage level(s)	1 application of 1 cm^2 StrataGraft per 1 cm^2 debrided wound. The dosage of StrataGraft is the total surface area of StrataGraft applied during any surgical procedure.
Route of Administration	StrataGraft is applied topically to complex skin defects that have been surgically excised to remove nonviable tissue. It is meshed up to 1:1, placed onto the wound bed, trimmed to fit the wound as necessary, and secured in place.
Dosing instructions	1 application of StrataGraft to wounds of 100 to 400 cm^2 in Cohort 1 or 400 to 1,900 cm^2 in Cohort 2, with applications overlaying meshed autograft
Manufacturer	Stratatech, a Mallinckrodt Company

7.2. Dose Modification

No dose modification is planned.

7.3. Method of Treatment Assignment

This study is designed as an open label, within-subject comparator study.

For randomization of Study Tx sites within each subject, an interactive voice randomization system will be used in this study and sites trained on its use.

For each subject, after excision/debridement is completed and the Study Tx sites are confirmed to meet Eligibility Criteria, comparable (ie, similar in both area and depth) Study Tx sites will be identified as A and B by the surgeon as outlined below:

- Treatment Site A will always be anterior, superior, proximal, lateral or to the subject's right
- Treatment Site B will always be posterior, inferior, distal, medial or to the subject's left

After anatomical assignment of Study Tx sites to Site A and Site B is completed per protocol definitions, Study Tx sites will be randomized to receive either:

1. Meshed autologous split-thickness skin graft (ie, AG Tx)
2. Meshed autograft overlaid with up to 1:1 mesh of StrataGraft (ie, SOMA Tx):
    a. 1 mesh ratio greater than the control site

b. 2 mesh ratios greater than the control site

7.4. Blinding

This study will be open label for the investigators performing the care of enrolled subjects, including the application of the Study Txs. All wound assessments, however, will be performed by a previously designated blinded assessor.

7.5. Preparation/Handling/Storage/Accountability

StrataGraft will be shipped to the study site on dry ice. Upon arrival, StrataGraft may be maintained in the sealed shipping container until the date and time indicated on this container. If the StrataGraft will not be used until after the date and time indicated on the shipping container, upon arrival at the site, StrataGraft should be transferred from the shipping container to a secure, ultra-cold (-70°C to -90°C) freezer with monitored temperature. Once StrataGraft has been received at the site, transferred into a site's ultra-cold freezer, any excursion from required storage range must be reported to the Sponsor as soon as it becomes known and prior to clinical use. Only subjects enrolled in the study may receive Study Tx and only authorized site staff may supply or administer Study Tx.

The investigator or the head of the medical institution (where applicable) is responsible for Study Tx accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the Study Tx preparation, handling, administration, and disposition of unused Study Tx are provided in a procedure manual.

7.6. Treatment Compliance

Study Tx may only be administered by a trained physician. All study staff and participating subjects and/or caregivers will be instructed on the appropriate care of the burn wounds treated with the study products. As this study incorporates the use of an intrapatient control, the two treatment sites are to be dressed/managed with the same regimen with exceptions being the use of a topical drug for suspected infection or another malady.

7.7. Concomitant Therapy

7.7.1. Concomitant Medications

Any medication or vaccine that the participant receives from the time of enrollment (ie, application of StrataGraft) until completion of study participation will be recorded, including name of drug, indication for administration, dates of administration, dose administered, and route of administration.

Intravenous fluids, anesthetic agents, vitamins, oral nutrition, and nutritional supplements are not considered concomitant medications for the purposes of this study and should not be entered into the Concomitant Medications.

7.7.2. Concomitant Therapies

All surgical procedures performed, including all autografting procedures, will be recorded, including date and the primary reason for the procedure. Additionally, all transfusions of whole blood, packed red blood cells, fresh frozen plasma, or platelets will be recorded, including date of transfusion, volume of transfusion, and indication for the transfusion.

After the treated wounds have healed, any use of compression garments, splints, or topical silicone sheet applications and any other scar prevention therapies will be recorded.

7.7.3. Prohibited Medications and Therapies

Subjects enrolled in this study may NOT receive the following for the duration of study participation:

- Dressings or wound washes applied to the treatment sites containing silver or sulfamylon (with active ingredient mafenide acetate) without thorough rinsing with saline prior to StrataGraft placement and no further use for duration of Study Tx
- ReCell™ use on any study Tx sites
- VAC therapy to the Study Tx sites
- Laser therapy to the Study Tx sites

8. DISCONTINUATION/WITHDRAWAL CRITERIA

Subjects are free to withdraw consent and discontinue participation in the study at any time. If a subject decides to discontinue participation, the reason(s) for discontinuation will be documented.

Subjects discontinued from the study due to an AE will be followed until the AE has resolved or is judged as clinically stable by the Investigator.

The investigator may discontinue a subject's participation at any time if s/he feels it is in the subject's best interest to be discontinued. Additionally, the subject may be considered lost to follow-up after 3 documented attempts are made to contact the subject.

All study data from withdrawn or discontinued subjects will be retained and used in the final study analyses.

9. STUDY ASSESSMENTS AND PROCEDURES

The Study Tx sites will be serially evaluated to assess wound healing progress.

9.1. Efficacy Assessments

9.1.1. Wound Closure

Complete wound closure is defined as complete skin re-epithelialization without drainage confirmed at 2 visits at least 2 weeks apart but no later than Week 20. Complete wound closure will be considered to have occurred at the earlier of the two observations of complete skin re-epithelialization without drainage. The blinded assessor will evaluate treatment site(s) and assess the proportion of the treated wound closed beginning at Day 7 and then daily, or as often as possible, during dressing changes until wound closure is achieved.

Durable wound closure is defined as persistence of closure, maintained for at least 3 months after the initial observation of closure (FDA, 2006). The blinded assessor will evaluate the wound sites at each visit subsequent to wound closure to assess the maintenance of the closure.

Both complete wound closure and durable wound closure will be assessed by direct clinician observation during a study visit. Confirmation of closure (ie, the visit 2 weeks after the first observation of closure), may be assessed by direct clinical observation or by subject-provided photographs, per Schedule of Activities (Table 1).

9.1.2. Study Site Photography

Photographs will be taken at each study visit to support clinical assessment of complete wound closure, durable wound closure, and adverse site events, as well as the POSAS/PSAQ assessments (ie, appearance and cosmesis) of the treatment sites.

Following hospital discharge, the subject will have the option to submit photographs of the Study Tx sites each week until Month 3, every other week until Month 6, and then monthly until the Month 12 visit. In the event that a subject is unable to travel to the study site for a visit or if a notable event has occurred between scheduled visits, photographs submitted may be used as evidence of wound characteristics. See the photo manual for specific instructions to obtain photographs.

9.1.3. Blinded Assessment of Treated Wound Sites

At each clinical study site, a primary and back-up assessor will be identified. These individuals will be tasked with assessing wound closure and once closed, the durability of that closure, and will be qualified to do so by training and clinical experience. Care should be taken to ensure these individuals remain blinded to the randomized treatment. Blinded assessment of all Study Tx wounds will begin on the Day 7 visit, and then daily, or as often as possible during dressing changes until the wound is completely closed, and then performed at each visit for the duration of that subject's study participation.

9.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities. Safety assessments will include monitoring of AEs, vital signs, laboratory values, incidence of wound-infection related events, and immunologic responses to StrataGraft.

9.2.1. Adverse Events (AEs)

All AEs that occur after the subject has signed the study ICF will be collected for the duration of their participation. It is anticipated that each subject will participate in this study for up to 14 months: up to 2 weeks of screening followed by up to 12 months (± 4 weeks) of post-treatment observation. See Appendix 4 for further description and information categorizing AEs.

9.2.2. Physical Examination and Medical History Review

A brief physical examination will be performed and will include, at a minimum, assessments of the skin (other than the burn injury), lungs (including any evidence of inhalation injury), cardiovascular system, and abdomen. As quality of the healed Study Tx sites is one of the primary endpoints, potential Study Tx sites with visible pre-existing scars should be excluded from consideration.

A medical history, including all previous surgical procedures and pregnancy history, where appropriate, will be solicited from the subject or abstracted from the medical record, with special attention given to any chronic illnesses existing prior to the burn injury.

9.2.3. Vital Signs

Vital signs will include temperature, systolic and diastolic blood pressure, and heart rate. Whenever possible, vital signs will be obtained using automated devices rather than manual methods.

9.2.4. Clinical Safety Laboratory Assessments

Laboratory assessments of CMP and CBC, as well as urine pregnancy tests for women of childbearing potential, will be performed at the local clinical laboratory of the clinical site. PRA and anti-bovine serum albumin (anti-BSA) antibody assessments will be performed by a central laboratory. A list of all clinical laboratory tests to be performed is provided in Appendix 2 and the Schedule of Activities notes the timing and frequency. It is preferable that, if possible, laboratory analyses required by this study are obtained in conjunction with other clinical necessary analyses and duplicative analyses are to be avoided.

The investigator will review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports will be maintained with the study source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study will be repeated as often as deemed clinically appropriate, until the values return to normal or baseline or are no longer considered clinically significant. Abnormal laboratory results are not, of themselves, AEs and will not be reported as such but identification of the root cause of the abnormality should be investigated, as it may be an AE.

9.2.5. Adverse Events of Special Interest

An Adverse Event of Special Interest (AESI), whether serious or nonserious, is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. AESI will be reported using the SAE/AESI Report Form and observe the same reporting timeline (Appendix 4). For this study, AESI include:

- Unexpected or unusual infections
- Dermatological malignancy

9.2.6. Other Safety Assessments

9.2.6.1. Incidence of Local Wound Events Including Infection

Study Tx sites will be examined by the investigator at each visit for signs of skin dyscrasias, such as vesicle or bullae formation, irritation, rash, dryness as well as signs of infection. Any noted issue will be reported as an AE.

Local Study Tx site infection will be determined by the clinical investigator and may include confirmatory microbiological assessment. Similarly, systemic infection will be determined by the clinical investigator and may include documentation of such signs as positive blood cultures, fever (defined as $\geq$38.5ºC) and/or elevated white blood cell count. Cultures of the treatment sites may be obtained for microbiological evaluation at the discretion of the clinical investigator or per institutional Standard of Care at any time during study treatment. The clinical investigator will evaluate the wound culture results for infections and their treatment will be documented in the electronic case report form (eCRF) with notation of specific location of the infection.

At investigator discretion, treatment of infected/suspected infected wound sites may include the use of targeted wound cleansing agents, topical antimicrobial agents and/or systemic antibiotics. Study wound sites may not be treated with any prohibited therapies, as outlined in Section 7.7.3.

9.2.6.2. Measures of Immunogenicity

Blood samples will be collected prior to placement of SOMA and again at Month 3 to assess changes in PRA and anti-BSA levels. PRA is a measure of antibody formation to non-self human proteins such as those found in StrataGraft. The cells in StrataGraft are cultured in media containing BSA and anti-BSA antibodies may be formed with exposure to StrataGraft. For further details, see the central laboratory manual.

9.2.6.3. Archival Sample Collection

In accordance with current xenotransplantation product guidelines, an archival sample will be collected at Baseline prior to StrataGraft placement. A small amount of blood (3mL) will be collected before StrataGraft application. This sample could be used as a baseline to assess health issues that may be related to treatment. These samples will be used only for the purpose of responding to a request from FDA. Both archival samples and any associated subject information will be stored and used only as required and allowed by law. For further details, see the central laboratory manual.

9.2.6.4. Histologic Assessment of Healed Tissue Characteristics

Subjects in Cohort 1 who have consented will have a biopsy obtained from their healed SOMA Tx site. A 3-mm punch biopsy will be harvested from the central section of the most right, lateral, and proximal area of the healed SOMA Tx wound. A second 3-mm punch biopsy will be taken from an area of uninjured skin adjacent to the healed SOMA Tx wound. The resultant wound will be managed per institutional standard.

The biopsy tissue will be examined using standard histologic techniques and assessed for characteristics such as architecture, presence of immune cells, elastin and collagen distribution.

For further detail, see the Manual of Procedures.

9.3. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

9.4. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.5. Biomarkers

No Biomarkers will be assessed in this study.

9.6. Health Care Resource Utilization (HCRU)

HCRU data that are associated with medical encounters will be reported in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Location of care for StrataGraft application (eg, inpatient hospital, outpatient/ambulatory hospital, clinic)
- Treatments used for all other non-study burn areas following excision and % TBSA treated with each
- Number and duration of operating room procedures required for study burn treatment
- Length of initial hospital stay and any readmissions

- Prescription drugs given for pain control
- Antibiotics given for outpatient use at discharge
- Whether a re-admission is planned
- Re-admission within 30 days after discharge

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

The sample size for the study is based on clinical experience. No calculations were performed to estimate sample size. Up to 40 subjects will be enrolled in 2 cohorts (detailed in Section 7).

10.2. Populations for Analyses

For purposes of analysis, the following analyses sets are defined:

Population	Description
Enrolled	All subjects who sign the ICF
Full analysis set (FSA)	All subjects who are randomized and treated with at least one area of SOMA Tx and one area of AG Tx. Efficacy analyses will be based on treatment applied (as treated).
Per-Protocol set (PPS)	All subjects in the FSA except for those who are excluded because of major efficacy-related protocol deviation. A major protocol violation is one that may affect the interpretation of study results. The criteria of major protocol deviations may include but is not limited to deviation from: • A patient who does not have primary endpoint value • Any major violations of efficacy-related entry criteria • Deviation of an inclusion or exclusion criterion Major protocol deviations will be reviewed case by case on a regular basis during the conduct of the study by the Medical Monitor and clinical trial management team and adjudicated before database lock.
Safety Analysis Set (SAF)	All subjects who sign the ICF and are treated with the investigational treatment are considered evaluable as the safety population.

10.3. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

The definition of primary and secondary endpoints is described in Section 4.

Safety assessments will include monitoring of AEs, vital signs, laboratory safety values, incidence of wound infection-related events, and immunologic responses to StrataGraft.

TEAE is defined as new or worsening AE after active Study Tx has been administered.

Safety assessments

1. Incidence of TEAE throughout study
2. Incidence of TEAE related to StrataGraft or Autografting procedure
3. Incidence of wound infection-related events at Study Tx sites
4. Clinically significant changes in vital signs throughout study compared to Baseline
5. Clinically significant changes in laboratory values between Baseline and Day 28

10.3.1. Advancement to Cohort 2

Following excision, a total of 20 subjects (Cohort 1) will be randomized into one of 2 groups:

- Group 1 subjects (n=10) will receive autograft (mesh ratio "m", chosen per clinical judgment) compared to m+1:1 meshed autograft overlaid with StrataGraft
- Group 2 (n=10) will receive meshed autograft (mesh ratio "m", per clinical judgment) compared to m+2:1 meshed autograft overlaid with StrataGraft, applied to wounds of 100 to 400 cm^2 in area.

Following completion of the Day 28 assessments, each subject will be determined to be a success or failure based upon the criteria below:

- % closed at Day 28, with success declared if the difference between paired wounds $\leq$ 10%, and
- Total score of Observer assessment of the POSAS at Day 28, with success declared if the difference between paired wounds $\leq$ 20%.

Group success will be declared if $\geq$80% subjects are determined to have treatment success within that group. Only one of the 2 SOMA Txs, m+1 or m+2, will be determined to meet the *a priori* established criteria above and become the SOMA Tx in Cohort 2.

10.3.2. Efficacy Analyses

Efficacy analyses will be performed comparing the differences between treatments within subjects, where appropriate. Descriptive summaries will be reported by treatment site, mesh ratio on SOMA Tx site, cohort and overall.

For calculated percent reduction of donor skin (as defined by [1-(AG Tx mesh ratio/SOMA Tx mesh ratio) × 100]) at Month 2, the log-transformation of the endpoint will be performed, and geometric mean ratio percent reduction of donor skin between treatment site will be presented.

In addition, the areas of treatment and donor sites will be summarized.

A mixed-effect model repeated measures method with covariates, including subject, treatment site, mesh ratio on SOMA Tx site, and cohort will be used for this log-transformed primary endpoint.

Analysis methods will be performed on the FSA, per-protocol set, and also on all observed data.

The summary statistics with 95% confidence interval, standard deviation, Least-squares means and the corresponding standard error will be presented for treatment site, mesh ratio, cohort and overall.

If the mixed-effect model repeated measures model does not converge or violates the model assumptions, the paired t-test will be used. If parametric statistics models are not appropriate, the Wilcoxon signed-rank test will be performed.

Graphs of Least-squares mean ± standard error and mean ± standard deviation by visit will be provided.

The same analysis method will be used for secondary efficacy continuous variables on FSA.

For the paired binary endpoint of difference in percent of SOMA Tx sites and AG Tx sites with complete wound closure without additional autografting at Month 2, 95% confidence intervals (CIs) of difference are derived by fitting a repeated measures model with PROC GENMOD that adjusts for the correlation with pairs, and then the 95% CI of difference can be estimated using the Margins Macro, provided by SAS. The P-value will be derived from McNemar's test, if applicable.

The descriptive statistics will also be performed by treatment site, mesh ratio on SOMA Tx site, cohort and overall and on FSA, per-protocol set, and all observed data. The missing binary data will be imputed as non-responders.

For other paired secondary efficacy binary endpoints, the same analysis as above will be used on FSA.

10.3.3. Safety Analyses

All safety analyses will be performed on the SAF.

AEs/TEAE will be coded using Medical Dictionary for Regulatory Activities by preferred term within system organ class. The number of TEAE/AEs, and the number of subjects reporting TEAE/AEs will be listed and summarized by body system, preferred term, severity, and causality and by Mesh ratios, cohort and treatment sites. All serious AEs (ie, SAEs) will be summarized by mesh ratios, cohort and treatment sites and narratives will be created. Overall, the incidence of wound infection-related events will be listed and summarized by mesh ratios, cohort, and treatment sites, if appropriate.

10.3.4. Concomitant Medication and Procedures

All concomitant medications and procedures will be listed by subject. All concomitant medications will be summarized by treatment and donor sites. The systemic concomitant medications away from treatment and donor sites will be summarized.

10.3.5. Interim Analyses

See Section 10.3.1.

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12. APPENDICES

Appendix 1: Abbreviations and Trademarks

Abbreviation or Special Term	Explanation
AE	Adverse event
AG	Autograft – a transplant from 1 location to another on same person
AG Tx	Autograft treatment – the control study treatment arm receiving the tissue application of meshed autograft alone
allograft	A transplant from 1 person to another person
anti-BSA	Anti-bovine serum albumin
CI	Confidence interval
CRF	Case report form
DPT	Deep partial-thickness
DSMB	Data and safety monitoring board
eCRF	Electronic case report form
FDA	Food and Drug Administration
FSA	Full analysis set
FT	Full-thickness
GCP	Good Clinical Practice
HCRU	Health care resource utilization
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional review board
POSAS	Patient and Observer Scar Assessment Scale
PRA	Panel reactive antibodies
PSAQ	Patient Scar Assessment Questionnaire
PPS	Per protocol set
SAE	Serious adverse event
SAF	Safety analysis set
SOMA	StrataGraft Overlay of Meshed Autograft
SOMA Tx	SOMA treatment - **S**trataGraft **O**verlay of **M**eshed **A**utograft (SOMA), where meshed autograft is covered with StrataGraft and applied to a burn area

Abbreviation or Special Term	Explanation
Study Tx	SOMA Tx and the control AG Tx
TBSA	Total body surface area
TEAE	Treatment-emergent adverse event
WOCBP	Women of childbearing potential

Appendix 2: Clinical Laboratory Tests

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td rowspan="4">Hematology (CBC)</td><td>Platelet Count</td><td rowspan="4">RBC Indices:
MCV
MCH
%Reticulocytes</td><td colspan="2" rowspan="4">WBC Count with Differential:
Neutrophils & Bands Lymphocytes
Eosinophils Monocytes Basophils</td></tr>
<tr><td>RBC Count</td></tr>
<tr><td>Hemoglobin</td></tr>
<tr><td>Hematocrit</td></tr>
<tr><td rowspan="3">Clinical Chemistry (CMP)</td><td>Total Protein</td><td>Potassium</td><td>Aspartate Amino-transferase (AST)</td><td>Total Bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Alanine Amino-transferase (ALT)</td><td>Direct Bilirubin</td></tr>
<tr><td>Glucose</td><td>Calcium</td><td>Alkaline phosphatase</td><td>Blood Urea Nitrogen (BUN)</td></tr>
<tr><td>Other Screening Tests</td><td colspan="4">Urine human chorionic gonadotropin (hCG) pregnancy test (in women of childbearing potential)</td></tr>
<tr><td colspan="5">NOTES:
The results of each test must be entered into the eCRF. Investigators must document their review of each laboratory safety report.</td></tr>
</table>

Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Committees Structure

An independent DSMB will be convened in order to ensure that the safety of subjects is adequately protected. The DSMB objectives, composition, and operational details of its activities will be defined in the DSMB Charter.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual

site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- All records, source documents, study worksheets, signed ICFs, and any other documents pertaining to the conduct of this study must be retained by the investigator for at least 2 years after study completion or approval of the drug, whichever comes last, unless local regulations or institutional policies require a longer retention period. (US 21CFR§312.62). No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition
An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

AE/SAE Recording
When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information in the CRF. It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE CRF page. There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to an agency. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. Moderate: An event that causes sufficient discomfort that it interferes with normal everyday activities. Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

The investigator will also consult the Investigator's Brochure (IB) in his/her assessment.

Relationships will be assessed as:

- Unrelated – no relationship between the AE/SAE and the administration of the study treatment; the AE/SAE can be explained by other etiologies, such as concomitant medications or the subject's clinical state
- Possibly related – an event that follows a plausible temporal sequence from administration of the study treatment, has a biologically causal relationship with the study treatment, or for which an alternate explanation for the AE/SAE is lacking. The event may have been produced by the subject's clinical state or other modes of therapy administered to the subject.
- Probably related – an event that follows a plausible temporal sequence from administration of the study treatment, has a biologically causal relationship with the study treatment, and for which the influence of alternate factors for the AE/SAE is unlikely.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to the Sponsor.**

The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

SAE and AESI Reporting
The primary mechanism for reporting an SAE and/or AESI to the Sponsor will be the electronic data collection tool. SAEs and AESI will be reported within 24 hours of first knowledge of the events. The initial report will include the completed SAE/AESI Form and any supporting documentation. Similarly, follow up reports will be submitted within 24 hours of receipt of follow up information on the Follow-up SAE/AESI Form. The site will enter the SAE and/or AESI data into the electronic system as soon as it becomes available. Contacts for SAE/AESI reporting can be found in the Manual of Procedures.

Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile.

Females who are postmenopausal age but are also on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of non-WOCBP before study enrollment.

Non-WOCBP Status

- Premenarchal
- Permanently sterile female is a premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). Note that in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Pregnancy Testing

Female participants of childbearing potential are eligible to participate in this study. All women of childbearing potential will be tested for pregnancy and if found to be pregnant, will be excluded from participation.

Collection of Pregnancy Information

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study, pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will continue with all scheduled study evaluations. Pregnant subjects will be followed until post-partum and the outcome of the pregnancy will be reported.

Appendix 6: Country-specific Requirements

This study is planned for clinical sites in the USA that adhere to ICH guidances and GCP. No country-specific requirements further affect this study protocol.

Appendix 7: Protocol Amendment History

The Summary of Changes presented below in Table 2 reflects the changes made in Amendment 5 and a high-level summary of the reason(s). Formatting, consistency, and minor editorial changes are not described.

Table 2: Summary of Changes

Formatting, consistency, and minor editorial changes are not listed.

Protocol section	Removed text in strikethrough and new text in bold	Issue/rationale for change
Summary of Changes for Amendments	Amendment **45** includes changes **related** to the ~~study timeline, identification~~ **FDA's revision** of ~~adverse events of special interest (AESI), Adverse Event Causality assessment~~ **the xenotransplantation requirements for StrataGraft** and ~~SAE/AESI reporting timeline as outlined in Appendix 7, which provides a~~ **minor administrative clarifications. A** complete summary of **the** changes **reflected in this protocol is provided in Appendix 7.**	Identifies the reason for changes and location of a complete summary of changes. Updated for current Protocol Amendment.
Table 1, Footnote f	[f] Blinded assessor will assess all treatment sites for percent re-epithelialization beginning at Day 7 and then daily, or as often as possible, during dressing changes, until complete closure~~, and then~~ **is observed. A second observation of complete closure at least 2 weeks after the initial observation is required to confirm closure. Thereafter, maintenance of closure will be assessed** at each study visit, to assess durability of closure.	Clarify definitions of confirmed complete closure and durable closure.

Protocol Section	Removed text is strikethrough and new test is in bold	Issue/rationale for change
Section 3.3	Results to date indicate that StrataGraft is well tolerated and no clinically observable allogeneic immune responses have been reported. The most common noted adverse reaction associated with StrataGraft treatment is pruritis. Theoretical risks specific to StrataGraft treatment include development of an immune response to the allogeneic cells of StrataGraft~~,~~ **and** the need for subsequent autografting of the StrataGraft treatment site~~, and the risk of exposure to a xenogeneic sourced infectious agent~~. **Because StrataGraft contains human cells, there is the possibility of transmission of an infectious agent. Additionally, StrataGraft contains glycerin, therefore in patients who have a glycerin sensitivity, there is a risk of an allergic reaction.** While no clinically relevant immune response to StrataGraft has been seen in STRATA2001, STRATA2011, STRATA2014 or STRATA2016, or there is a theoretical possibility that subjects who mount an immune response to the allogeneic cells of StrataGraft and who then become candidates for receiving solid organ transplants could experience of narrowing of the suitable donor pool. Data from STRATA2001 showed the autograft take after treatment of the wound bed with StrataGraft was similar to cadaver allograft, 97% and 96%, respectively. Additionally, the 2 STRATA2011, the 3 STRATA2014 and the 3 STRATA2016 subjects who received autograft at sites previously treated with StrataGraft showed complete wound closure before or at Month 3, demonstrating that treatment with StrataGraft does not impede achievement of wound closure in the event autograft is used to achieve definitive closure.	Reflects modifications of the xenotransplantation product prohibitions/requirements for StrataGraft as granted by the US FDA

Protocol Section	Removed text is strikethrough and new test is in bold	Issue/rationale for change
Section 3.3	~~The last theoretical risk that of a xenogeneic response, is due to an historic exposure of the NIKS keratinocytes to live murine cells during in vitro culture. NIKS keratinocytes were initially isolated and expanded on replication inactivated murine 3T3M1 cells that served as a source of factors supporting cellular growth. These "feeder cells" were thoroughly tested, shown to be free of all tested diseases, and are no longer used to support the growth of the NIKS keratinocytes, nor used in the manufacturing process.~~ ~~StrataGraft is an allogeneic, cellularized scaffold product. The construct consists of differentiated epidermal layer of human keratinocytes (near diploid human keratinocytes (NIKS) grown on a dermal layer of gelled collagen embedded with normal human dermal fibroblasts.~~ **StrataGraft is a xenotransplantation product because in the past, one of the cell types used to make StrataGraft was grown with mouse cells. The cell banks have been tested and found to be free of detectable infectious agents and mouse cells are no longer used in the manufacture of StrataGraft. There have been no identified health concerns associated with these mouse cells.** **Recipients of xenotransplantation products are generally not eligible, per federal regulations, to donate whole blood, blood components, source plasma or source leukocytes. However, individual blood banks may request an exception from FDA. StrataGraft recipients wishing to donate blood or blood products should check with their donation center. StrataGraft recipients who otherwise meet the donor requirements are eligible to donate human cells, tissues, breast milk, ova, sperm or body parts for transplantation.**	Reflects modifications of the xenotransplantation product prohibitions/requirements for StrataGraft as granted by the US FDA

Protocol Section	Removed text is strikethrough and new text is in bold	Issue/rationale for change
Section 1 and Section 4	(Within Co-Primary Endpoints) • Difference in percent of SOMA Tx sites and AG Tx sites with **confirmed** complete wound closure without additional autografting at Month 2 (Within Secondary Endpoints) • Incidence of **confirmed** complete wound closure of the Study Tx sites at Days 14, 21, 28, and 42, Month 2 and Month 3	Clarify that endpoints include confirmed complete wound closure, not simple closure
Section 5.6	In this study, safety will be monitored by the Medical Monitor and Global Safety Lead from the Sponsor, as well as the Data Safety Monitoring Board (DSMB). The DSMB will be independent of study conduct. Subject enrollment will be paused pending discussion with DSMB if any of the following occur: • ~~Infection~~ **Unexpected infection** at the StrataGraft treated site ~~attributed~~ **that is possibly or probably related** to StrataGraft **and is an SAE** • Severe acute hypersensitivity reaction attributed to StrataGraft • Death attributed to StrataGraft	Clarified the type of infection that merits an Adverse Event of Special Interest
Section 7.1	Dosage formulation: StrataGraft is ~~an~~ **a viable and metabolically active** allogeneic~~,~~ **human NIKS keratinocytes and human dermal fibroblasts** cellularized **layered** scaffold ~~product~~. It is ~~grown~~ **supplied** in a rectangular, 100 cm^2 format, ~~and supplied~~ loosely adherent to a polycarbonate membrane of a tissue insert. StrataGraft is stored at -70°C to -90°C until thawed for use. ~~Packaging and Labeling:~~ ~~StrataGraft is a cryopreserved, sterile, cream colored, rectangular, living skin equivalent with a surface area of approximately 100 cm2 per unit that may be meshed, stapled, glued and/or sutured.~~	Align description with the package insert

Protocol section	Removed text in strikethrough and new text in bold	Issue/rationale for change
Section 7.5	~~StrataGraft will be supplied frozen to the Investigator in an appropriate shipper. The investigator or designee must confirm appropriate temperature conditions have been maintained during storage and transit for all Study Tx received and any discrepancies are reported and resolved before use of the Study Tx.~~ ~~Once received and each StrataGraft piece logged, the product will be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.~~ **StrataGraft will be shipped to the study site on dry ice. Upon arrival, StrataGraft may be maintained in the sealed shipping container until the date and time indicated on this container. If the StrataGraft will not be used until after the date and time indicated on the shipping container, upon arrival at the site, StrataGraft should be transferred from the shipping container to a secure, ultra-cold (-70°C to -90°C) freezer with monitored temperature. Once StrataGraft has been received at the site, and transferred into a site's ultra-cold freezer, any excursion from required storage range must be reported to the Sponsor as soon as it becomes known and prior to clinical use.** Only subjects enrolled in the study may receive Study Tx and only authorized site staff may supply or administer Study Tx.	Update shipping and receipt of StrataGraft.

Protocol section	Removed text in strikethrough and new text in bold	Issue/rationale for change
Section 9.2.5	An ~~adverse event~~ **Adverse Event** of ~~special interest (~~**Special Interest (AESI), whether** serious or non-serious~~)~~, is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. **Adverse Events of Special Interest** (AESI) will be reported using the SAE/AESI Report Form and observe the same reporting timeline (Appendix 4). For this study, ~~Adverse Events of Special Interest (~~AESI~~)~~ include: • Unexpected or unusual infections • Dermatological malignancy • ~~Any xenotransplantation related adverse event or clinical event that is suspicious of a xenogeneic cause, e.g. disease/disorder of known zoonotic origin.~~	Clarification of language, and reflects modifications of the xenotransplantation product prohibitions/requirements for StrataGraft as granted by the US FDA

Protocol section	Removed text in strikethrough and new text in bold	Issue/rationale for change
Section 9.2.6.1	Study Tx sites will be examined by the investigator at each visit for signs of skin dyscrasias, such as vesicle or bullae formation, irritation, rash, dryness as well as signs of infection. Any noted issue will be reported as an AE. Local Study Tx site infection will be determined by the clinical investigator and may include confirmatory microbiological assessment. Similarly, systemic infection will be determined by the clinical investigator and may include documentation of such signs as positive blood cultures, fever (defined as ≥38.5°C) and/or elevated white blood cell count. Cultures of the treatment sites may be obtained for microbiological evaluation at the discretion of the clinical investigator or per institutional Standard of Care at any time during study treatment. The clinical investigator will evaluate the wound culture results for infections and their treatment will be documented in the electronic case report form (eCRF) with notation of specific location of the infection. **At investigator discretion, treatment of infected/suspected infected wound sites may include the use of targeted wound cleansing agents, topical antimicrobial agents and/or systemic antibiotics. Study wound sites may not be treated with any prohibited therapies, as outlined in Section 7.7.3.**	Clarified instructions related to treatment of infections. Linked to Prohibited Medications and Therapies section.

Protocol section	**Removed text in strikethrough and new text in bold**	**Issue/rationale for change**
Section 9.2.6.3	In accordance with current xenotransplantation **product** guidelines, an archival sample will be collected at Baseline prior to StrataGraft placement. **A small amount of blood (3mL) will be collected before StrataGraft application. This sample could be used as a baseline to assess health issues that may be related to treatment. These samples will be used only for the purpose of responding to a request from FDA. Both archival samples and any associated subject information will be stored and used only as required and allowed by law**. For further details, see the central laboratory manual.	Clarifying the storage duration and use of collected archival samples.
Section 9.6	Health ~~**Economics Research**~~ **Care Resource** Utilization **(HCRU)**	Updating Section title with correct nomenclature

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Approval Task	[redacted] 28-Sep-2023 18:58:01 GMT+0000

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