Official Title: A Multicenter, Open-label, Study of StrataGraft Skin Tissue in Adult Subjects with Deep Partial-thickness Thermal Burns

NCT Number: NCT04123548

Document Date: Protocol Amendment 1 (Version 2.0): 02 October 2020

STRATAGRAFT® SKIN TISSUE

A MULTICENTER, OPEN-LABEL, STUDY OF STRATAGRAFT® SKIN TISSUE IN ADULT SUBJECTS WITH DEEP PARTIAL THICKNESS THERMAL BURNS

Protocol Number: MNK01053115

Regulatory Agency Identifying Number (IND): 010,113

Original Protocol, Version 1, dated 26 August 2019

Amendment 1 (Version 2.0), dated 02 October 2020

Short Title: StrataCAT

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

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 guidance documents and regulations including, but not limited to:

- International Council for Harmonisation (ICH) E6(R2): Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice, which has its ethical foundation in the Declaration of Helsinki
- the US Code of Federal Regulations (CFR) (as appropriate, including 42 CFR 11: Final Rule for Clinical Trials Registration and Results Information Submission)
- NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information
- all applicable national and local regulations (as appropriate, including the European Clinical Trials Regulation)
- protections for privacy (as appropriate, including the European General Data Protection Regulation
- provisions of all local ethics committees

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] MD, MPh, MBA

[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 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® skin tissue

STUDY:

Protocol MNK01053115

Protocol Version 2 Amendment 1

PRINCIPAL/COORDINATING INVESTIGATOR(S)

Name:

Title:

SIGNATURE_____DATE: _____

1. SYNOPSIS

Name of Sponsor/Company: Stratatech, a Mallinckrodt Company		
Name of Investigational Product: StrataGraft® skin tissue		
Name of Active Ingredient: Viable and metabolically active allogeneic human (near-diploid human keratinocytes [NIKS]) and human dermal fibroblasts		
Protocol Number: MNK01053115	**Phase:** 3b	**Country:** USA
Title of Study: A Multicenter, Open-label, Study of StrataGraft® Skin Tissue in Adult Subjects with Deep Partial-Thickness Thermal Burns		
Study Center(s): Multicenter		
Study Period: 24 Weeks Estimated date first subject enrolled: November 2019 Estimated date last subject completed: 24 weeks afte the date of the occurrence of either commercial availability of the product or Sponsor closure of the study, whichever comes first.		**Phase of development:** 3b

Study Objective(s)/Endpoint(s)/Outcome Measures(s)

Primary Objective(s)/Endpoint(s)

Primary Objective	Primary Endpoint
Demonstrate the safety of a single appli ation of StrataGraft skin tissue in the post-excision treatment of deep partial-thickness (DPT) thermal burns that contain intact dermal elements.	Count and percent of subjects with treatment-emergent adverse events (TEAEs)

Primary Outcome Measure:

Title:

Number of participants with TEAEs during the study

Description:

Total count of participants with TEAEs during the study

Timeframe:

Approximately 24 weeks

Other Pre-specified Objective(s)/Endpoint(s):

Other Objective(s)	Other Endpoint(s)
Demonstrate the clinical outcomes of a single application of StrataGraft skin tissue in the post excision treatment of thermally induced DPT burns that contain intact dermal elements.	• Proportion of subjects with confirmed wound closure without autograft placement (ie, complete re-epithelialization without drainage and subsequently verified with confirmation assessment) on or before Week 12 and supported by photo-documentation • Proportion of subjects with confirmed wound closure without autograft (verified with confirmation assessment) at each visit and supported by photo-documentation • Proportion of subjects without autografting who maintain durable wound closure by Week 24 • Time to confirmed wound closure without autografting (verified with confirmation assessment) • Treatment site skin quality data: The total observed POSAS by clinician and by subject. Per site descriptive statistics will be presented separately for clinician and subject values for each of the individual POSAS items and the total POSAS score, represented as the mean score across all treatment sites and supported by photo-documentation. • Number (%) of subjects with wound infection-related events

Exploratory Objective(s)/Endpoint(s):

Exploratory Objective	Exploratory Endpoint
Assess for healthcare resource utilization (HCRU) throughout the study period	• Location of care for StrataGraft application (eg, inpatient hospital, outpatient/ambulatory hospital, clinic, etc.) • Treatments used for all other burn areas following excision and % total body surface

	area (TBSA) treated with each (other than StrataGraft treatment sites) • Number of Operating Room (OR) procedures required for burn treatment: excisions, application of StrataGraft tissue and all other grafting procedures, including autografts, allografts, and xenografts • Duration of each OR procedure • Length of hospital stay • Prescription drugs given at discharge from the hospital for wound-related events including pain control, itch, psychotropics, and antibiotic • Re-admission within 30 days after discharge • Whether a re-admission is planned • Length of hospital stay of re-admission

Study Design: This is a prospective, open-label, single-arm study assessing the safety and clinical outcomes of StrataGraft skin tissue in the treatment of DPT thermal burn injuries with intact dermal elements. Study enrollment will be approximately 100 subjects but will continue until StrataGraft becomes commercially available or until th Sp nsor decides to close the study. Enrollment will include subjects with a minimum of 3% and up to 50% TBSA of partial +/- full thickness thermal burn. Treatment will include a single pplic tion of up to 1:1 meshed StrataGraft skin tissue on DPT wound(s) totaling no more than approximately 2000 square centimeters in area (no more than 3 study treatment thermal burn areas and no more than 20 StrataGraft tissues applied to the study treatment areas). The wound bed must be cle n, excised and have bleeding controlled prior to StrataGraft tissue application. The tissues may be anchored with tissue adhesive, staples, or sutures, covered with a nonadherent, nonocclusive contact layer and additional secondary dressings per institutional standard of care (dressings should not contain silver). Safety assessments will include monitoring of TEAEs, serious adverse events (SAEs), wound infections, and clinically significant vital signs, laboratory test results, and immunological changes. Wound assessments will include measurements for average depth, length, and width for calculations of area and percent epithelialization. Wound assessments will be facilitated by photographs taken by the subject and/or taken by the clinical study site staff at study visits throughout the study. Scar evaluation using the POSAS will be conducted. Additionally, HCRU data will be collected. All subjects eligible to be consented throughout the duration of the study following application of StrataGraft skin tissue to be part of a contact database and follow-up registry; subjects will have the choice to decline with no impact to their participation in the study. In addition, a subset of 10 subjects (sourced from across all the sites) with closed wounds will be separately consented to have a punch biopsy (measuring 3 mm) taken from the center of the healed burn wound, and another punch biopsy measuring 3 mm taken from non-burned healthy skin. A histological evaluation of both samples will be done to analyze and contrast the skin architecture in the healed burn wound with healthy skin. The biopsy will happen at the study visit Week 12, regardless of when wound closure occurs.

Methodology: The data generally will be summarized with descriptive statistics. The Kaplan-Meier estimate will be performed to determine time to confirmed wound closure.

Sample Size Justification: No sample size determinations were performed for this study.

Number of subjects (planned): approximately 100

Diagnosis: Thermally induced DPT burns that contain intact dermal elements and for which surgical excision and autograft are clinically indicated

Inclusion Criteria:

Subject-specific criteria:

1. Men and women ≥ 18 years
2. Written informed consent
3. Sufficient healthy skin identified and designated as a donor site in the event that the StrataGraft treatment site requires autografting
4. 3% up to <50% TBSA of partial +/- full thickness th rmal burns

Treatment site-specific criteria:

5. Thermal burn(s) with intact dermal elements for which excision and autografting are clinically indicated
6. Total treatment areas no more than approximately 2000 cm^2 and total tissues no more than 20 tissues. Total burn may consist of up to 3 noncontiguous burn sites
7. First excision and grafting of study treatment sites
8. Thermal burn(s) on the torso, upper extremities, and lower extremities

Exclusion Criteria:

Subject-specific criteria:

1. Pregnant women
2. Prisoners
3. Subjects receiving systemic immunosuppressive therapy at the time of injury
4. Subjects with a known history of malignancy
5. Pre-admission insulin-dependent diabetic subjects
6. Subjects with concurrent conditions that, in the opinion of the investigator, may compromise subject safety or study objectives
7. Expected survival of less than 3 months
8. Participation in a study of an investigational device, pharmaceutical, or biologic drug within 90 days prior to enrollment

   (Participants in nutritional or non-interventional observational studies where no investigational product or device is given or administered will not be excluded.)

Treatment site-specific criteria: 9. Full-thickness burns 10. Chronic wounds 11. The face, head, neck, hands, feet, digits, buttocks, perineum/genitals, and areas over joints 12. Treatment sites immediately adjacent to unexcised eschar 13. Clinical or laboratory determination of infection at the anticipated treatment sites at time of StrataGraft placement
Investigational Product, Dosage and Mode of Administration: StrataGraft skin tissue is applied once to no more than 3 noncontiguous burn sites, totaling a maximum study treatment area of no more than approximately 2000 cm^2, and using no more than 20 tissues.
Duration of Treatment: Subject evaluated for 24 weeks after the StrataGraft skin tissue placement
Reference Therapy, Dosage and Mode of Administration: None
Statistical Methods: For all safety assessments, the data will be summarized with descriptive statistics. For all other outcomes, the data will be summarized with descriptive statistics and some of these with 95% confidence intervals. The Kaplan-Meier estimate will be computed to determine the median time to confirmed wound closure without autog ft placement (verified with confirmation assessment). No hypothesis testing will be conducted.

SUMMARY OF CHANGES FOR AMENDMENTS

Amendment 1 was primarily initiated due to the need for provisions for publicly stated emergencies. Additionally, DSMB safety monitoring has been replaced with monitoring by a Sponsor Safety Committee, safety laboratory assessments added, and clarification added for wound assessments, for collection of photographs, for collection of data for prescription medications plus other minor changes and administrative changes. Appendix 1 provides all changes in detail.

2. TABLE OF CONTENTS AND LIST OF TABLES

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3. ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are referenced by this study protocol as presented in Table 1.

Table 1: Abbreviations and Special Terms

Abbreviation or Special Term	Explanation
AE	Adverse event
allograft	A transplant from 1 person to another person
autograft	Transplant of skin tissue from 1 location to another on same person
CFR	Code of Federal Regulations
DPT	Deep partial-thickness (has intact dermal elements)
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCRU	Health care resource u ilization
HLA	Human leukocyte a tigen
ICH	International Council for Harmonisation
IEC	Independent Ethic Committee
IRB	Institutional revi w board
mITT	Modified intention-to-treat
NIKS	Near-diploid human keratinocytes
OR	Operating Room
POSAS	Patient and observer scar assessment scale
PRA	Panel reactive antibodies
SAE	Serious adverse event
SoC	Standard of Care
TBSA	Total body surface area
TEAE	Treatment-emergent adverse event
xenograft	The transplant of an organ, tissue, or cells to an individual of another species.

4. INTRODUCTION

Every year in the United States, approximately 45,000 patients experience burns that require them to be hospitalized, and of those individuals approximately 10 to 20% require surgical intervention such as autografting (American Burn, 2016). Depending upon the severity of the injury, hospitalization can often be protracted. Based on data in the 2017 National Burn Repository Annual Report, which includes data collected from 101 US burn centers in 37 states and the District of Columbia between 2008 and 2017, representing a cross-section of US hospitals, the average length of stay for survivors was slightly greater than 1 day per %TBSA burned (American Burn Association, 2017).

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 infection 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 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 (Muller, 1994; Herndon, 1989), 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 chronic scarring at those sites. As such, methods to reduce the amount of d nor tissue needed to achieve wound closure are always sought.

4.1. Study Rationale

StrataGraft skin tissue is an allogeneic tissue-engineered product. StrataGraft skin tissue is under development by Stratatech Corpo tion, the Sponsor Company, as an alternative to autografting in the closure of thermal burns containing intact dermal elements.

Clinical data from adults suggest that treatment of DPT thermal burns with StrataGraft tissue can result in wound closure while reducing or eliminating the need for autograft. Clinical data have also shown that this tissue construct does not transplant but is replaced by the subject's cells as the wound heals (Sponsor unpublished data).

This study is being conducted in order to provide continued access to StrataGraft skin tissue for clinical sites following the closure of enrollment to the STRATA2016 study. This study will collect safety and clinical outcomes in a population of subjects with thermally induced DPT burns that contain intact dermal elements.

This study will be conducted in compliance with applicable regulations and guidance related to GCP and in compliance with this protocol.

4.2. Assessment of Potential Risks and Benefits

Results to date indicate that StrataGraft skin tissue is well tolerated, and no acute clinical signs or symptoms of an allogeneic immune response have been reported. The most common noted adverse reaction associated with StrataGraft is pruritus.

Subjects in this study will undergo surgical excision of the burn area. The risks associated with the surgical procedure include pain and bleeding at the surgical site as well as potential complications of anesthesia, such as nausea/vomiting, chills, and sore throat. A subset of 10 subjects who achieve complete wound closure and have consented to study treatment will also undergo a biopsy of their healed StrataGraft-treated wound sites at Week 12 to histologically assess tissue architecture and any other histological tests as required. The risks associated with the procedure include those associated with application of a local anesthetic as well as pain or discomfort, bleeding, infection, and scarring at the biopsy site. All procedures and activities in this study, other than the actual application of StrataGraft tissue and skin biopsy, are generally accepted as standard of care (SoC) for subjects with thermal burns and do not present any increased risk to the subjects.

StrataGraft skin tissue is a viable, bilayer, allogeneic human skin substitute composed of a fully stratified epithelial layer comprised of NIKS keratinocytes from a single human donor grown on a dermal equivalent comprised of purified Type I animal collagen containing normal human fibroblasts from a second donor. During development of the NIKS keratinocytes, these cells were previously exposed to murine feeder cells. These feeder cells were derived from a single source, thoroughly tested, and found to be free f detectable adventitious agents. [redacted] To comply with current Food and Drug Administration (FDA) xenotransplantation guidelines, [redacted] (FDA, 2016; Bloom, 2000) archival blood samples will be collected at baseline and retained in accordance with FDA guidelines.

The benefit of treating burns wi h StrataGraft skin tissue is that the viable cells of StrataGraft tissue produce and secrete a variety of growth factors, cytokines, and antimicrobial peptides that are collectively anticipated to facilitate wound repair and tissue regeneration.

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

4.3. Summary of Relevant Clinical Studies

Previous studies in adults with DPT thermal burns have demonstrated that StrataGraft skin tissue is generally safe with salutary clinical outcomes in regard to closure of DPT burns and elimination of autograft placement in the majority of subjects.

The Phase 1b study, "Open-label, Controlled, Randomized, Multicenter, Dose Escalation Study Evaluating the Safety and Efficacy of StrataGraft® Skin Tissue in Promoting the Healing of the Deep Partial-Thickness Component of Complex Skin Defects as an Alternative to Autografting," (STRATA2011) was an open-label, dose-escalation, multicenter study evaluating the safety, tolerability, and efficacy of StrataGraft skin tissue in promoting the healing of complex skin defects containing intact dermal elements. In this study, StrataGraft skin tissue was applied once to DPT burns to assess autologous tissue regeneration with reduction or elimination of

autografts. This study included subjects with thermal burns of 3 to 49% TBSA. Each subject had 2 comparable burn wound areas identified, excised to remove nonviable tissue, and randomized to receive StrataGraft skin tissue or autograft. Thirty subjects were enrolled with 10 subjects in Cohort 1 receiving up to 220 cm^2 of refrigerated StrataGraft skin tissue and 10 subjects in Cohort 2 receiving up to 440 cm^2 of refrigerated StrataGraft skin tissue. Ten subjects in Cohort 3 received up to 440 cm^2 of thawed cryopreserved StrataGraft skin tissue. None of the subjects treated with StrataGraft skin tissue exhibited any significant safety concerns and none underwent autografting prior to Day 28. Additionally, 27 of the 28 per-protocol subjects (96%) exhibited complete wound closure of StrataGraft treatment sites at Month 3. Molecular analysis of biopsies taken from treated wound sites at Month 3 demonstrated no evidence of StrataGraft skin tissue DNA, indicating that the cellular components of StrataGraft skin tissue were no longer present.

The Phase 3 study "A Multicenter, Open-Label, Randomized Comparison of the Efficacy and Safety of StrataGraft Skin Tissue vs Autograft in Adult Subjects with Thermal Burns" (STRATA2016) is an open-label, controlled, randomized, multicenter study evaluating the efficacy and safety of StrataGraft skin tissue in the treatment of complex skin defects due to thermal burns that contain intact dermal elements and for which surgical excision and autografting are clinically indicated. The number of enrolled subjects was 71 and the last subject completed all study procedures in March 2020. No Stra aGraft-related SAEs were reported.

5. STUDY OBJECTIVES AND PURPOSE

5.1. Primary Objective

The primary objective of this study is to assess the safety of a single application of StrataGraft skin tissue in the treatment of adults with thermally induced DPT burns that contain intact dermal elements.

Primary Objective(s)/Endpoint(s)/Outcome(s)

Primary Objective	Primary Endpoint
Demonstrate the safety of a single application of StrataGraft skin tissue in the post excision treatment of thermally induced DPT burns that contain intact dermal elements.	Count and percentage of subjects with TEAEs

5.2. Other Objective(s)

Other pre-specified endpoints will be assessed throughout the study period.

Other Pre-specified Objective(s)/Endpoint(s)

Other Objective	Other Endpoints
Demonstrate the clinical outcomes of a single application of StrataGraft skin tissue in the post excision treatment of thermally induced DPT burns that contain intact dermal elements.	• Proportion of subjects with confirmed wound closure without autograft placement (ie, complete re-epithelialization without drainage and subsequently verified with confirmation assessment) on or before Week 12 and supported by photo-documentation • Proportion of subjects with confirmed wound closure without autograft (verified with confirmation assessment) at each visit and supported by photo-documentation • Proportion of subjects without autografting who maintain durable wound closure by Week 24 • Time to confirmed wound closure without autografting (verified with confirmation assessment) • Treatment site skin quality data: The total observed POSAS by clinician and by subject. Per site descriptive statistics will be presented separately for clinician and subject values for each of the individual POSAS items and the

	total POSAS score, represented as the mean score across all treatment sites and supported by photo-documentation • Number (%) of subjects with wound infection-related events

5.3. Exploratory Objectives

Information for HCRU will be assessed throughout the study period.

Exploratory Objective(s)/Endpoint(s)/Outcome(s)

Exploratory Objective	Exploratory Endpoint
HCRU assessments	• Location of care for StrataGraft application (eg, inpatient hospital, outpatient/ambulatory hospital, clinic, etc.) • Treatments used for all other burn areas following xcision and % TBSA treated with each (other than StrataGraft treatment sites) • Number of Operating Room (OR) procedures required for burn treatment: excisions, application of StrataGraft tissue and all other grafting procedures, including autografts, allografts, and xenografts • Duration of each OR procedure • Length of hospital stay • Prescription drugs given at discharge from the hospital for wound-related events including pain control, itch, psychotropics, and antibiotics • Re-admission within 30 days after discharge • Whether a re-admission is planned • Length of hospital stay of re-admission

5.4. Subgroup Analyses

Subgroup analyses include race (white, non-white), ethnicity, age (<65, ≥ 65), sex (male, female), size of area treated with StrataGraft (≤ 500 cm^2, > 500 cm^2), and overall TBSA of wound burden defined as burns TBSA plus donor site area (< median, ≥ median).

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a Phase 3b, open-label, multicenter study of adults evaluating the safety and clinical outcomes of StrataGraft® skin tissue in the treatment of thermally induced DPT burns that contain intact dermal elements.

No randomization will be conducted for the study, as this study is designed to be a single arm study.

Subjects may be assessed to have no more than 3 noncontiguous burn areas treated and receive no more than 20 tissues of StrataGraft skin tissue (for a total StrataGraft skin tissue treated area of no more than approximately 2000 cm^2).

The primary endpoint is count and percent of subjects with TEAEs.

Other endpoints include:

- The proportion of StrataGraft skin tissue-treated wound area with confirmed wound closure without autograft placement (ie, complete re-epithelialization without drainage and subsequently verified by confirmation assessment) on or before Week 12 and supported by photo-documentation.
- The proportion of subjects with confirmed wound closure without autograft placement (verified with confirmation assessment) at each visit and supported by photo-documentation.
- The proportion of subjects without autografting achieving and maintaining durable wound closure by Week 24. Durable wound closure is achieved when a wound is observed as remaining closed at l ast 3 months after complete wound closure.
- The time to confirmed wound closure without autograft placement (verified with confirmation assessment). For in-person visits, the investigator will assess the wound in person or alternatively assess a photo provided by the subject if the subject misses a visit. For the weeks in-between onsite visits, the subject will have a photo taken and send them to a photo repository beginning at discharge then weekly until Week 12 and then every other week until Week 24. These photos will also be assessed by the principal investigator.
- Skin quality and cosmesis assessments at Week 12 and Week 24 by the subject and observer using POSAS scores; these assessments will be supported both by photo-documentation and POSAS scores.
- Number (%) of subjects with wound-infection related events.

The exploratory endpoints include collection of information for HCRU:

- Location of care for StrataGraft application (eg, inpatient hospital, outpatient/ambulatory hospital, clinic, etc.)
- Treatments used for all other burn areas following excision and %TBSA treated with each (other than StrataGraft treatment sites)
- Number of OR procedures required for burn treatment: excisions, application of StrataGraft tissue and all other grafting procedures, including autografts, allografts, and xenografts
- Duration of each OR procedure
- Length of hospital stay
- Prescription drugs given at discharge from the hospital for wound-related events including pain control, itch, psychotropics, and antibiotics
- Re-admission within 30 days after discharge
- Whether a re-admission is planned
- Length of hospital stay of re-admission

6.1.1. Schedule of Assessments

The study assessments are presented by visit in Table 2.

Table 2: Schedule of Assessments

Procedure	Screening +/-14 days	Day 1 Baseline	Week 1[a] ± 2 days	Week 2[a] ± 2 days	Week 4[a] ± 3 days	Week 8[b] ± 3 days	Week 12[b] ± 7 days	Week 24[b] ± 7 days	Visit for Confirmation of Healing[c]
Informed consent for study treatment	√								
Consent for direct contact by Sponsor and safety registry post study [d]		√--	------ ---	----------	-----√----	----------	----------	----------	------√
Medical history, physical examination, and height and weight	√								
Pregnancy test	√								-
Vital signs	√	√	√	√	√	√	√	√	√
Infection assessment	√	√	√	√	√	√	√	√	√
Concomitant medications/procedures	√	√	√	√	√	√	√	√	√
Prescription drugs given at discharge from the hospital for wound-related events including pain control, itch, psychotropics, and antibiotics		√	√	√	√	√	√	√	√
Safety laboratory tests[e]		√[f]					√		
Archival plasma and leukocyte collection		√							

Procedure	Screening +/-14 days	Day 1 Baseline	Week 1[a] ± 2 days	Week 2[a] ± 2 days	Week 4[a] ± 3 days	Week 8[b] ± 3 days	Week 12[b] ± 7 days	Week 24[b] ± 7 days	Visit for Confirmation of Healing[c]
Blood collection for PRA testing (HLA I and II)		√			√		√		
StrataGraft skin tissue application		√							
AE[g] /SAE /TEAE assessment	√	√	√	√	√	√	√	√	√
Photograph of treatment sites[h]	√	√	√	√	√	√	√	√	√
Assessment of wound closure/continued closure			√	√	√	√	√	√	√
Skin quality outcome of treatment sites							√	√	
HCRU Assessments	√	√	√	√	√	√	√	√	√
Biopsies[i]							√		

[a] In public state of emergency situations, the Weeks 1 and 2 visit windows can be expanded to include ± 5 days.
[a] In public state of emergency situations, the Week 4 visit window an b expanded to include ± 12 days.
[b] In public state of emergency situations, the Weeks 8, 12, and 24 visit windows can be expanded to include ± 14 days.
[c] This visit may be scheduled at any time during the study to occu at least 2 weeks after initial observation of complete wound closure.
[d] Consent for post study registry can be obtained at any study visit beginning at Screening (together with the consent for the study treatment), during the study treatment, or at the final study visit.
[e] Any testing abstracted from the medical record from the time of admission throughout the study treatment period.
[f] May be performed within 48 hours of surgery.
[g] AEs will be assessed on an ongoing basis; AEs (serious and non-serious) occurring from time of signing informed consent until completion of the Final Visit and follow-up until resolution of any ongoing TEAE at the time of study treatment completion or subject withdrawal.
[h] A weekly photo taken by subject (or designate) of the treatment site(s) for the first 12 weeks and then every other week to Week 24. Photos submitted during a week when there's no in-person visit would serve as an allowable proxy for observing wound characteristics. If a subject's wound is noted to be closed for the first time via a submitted photo that should prompt a confirmation of wound healing visit 2 weeks later.
[i] Biopsies of a closed wound and of the normal skin will be taken from a subgroup of 10 subjects.

6.1.2. Study Design Rationale

This Phase 3b, open-label study provides the opportunity of continuing access of StrataGraft skin tissue at clinical study sites that participated in the prior Phase 3 study. Safety assessments and clinical outcomes will be collected and analyzed to supplement the safety information regarding this product, allow for collection of health economic data, and provide additional efficacy outcomes data.

6.1.3. Treatment Rationale

Observations in prior clinical studies suggest that StrataGraft skin tissue may promote healing of DPT burns with intact dermal elements. In prior studies with StrataGraft skin tissue in this population, no clinically important untoward effects have been associated solely with treatment with StrataGraft skin tissue.

6.1.4. End of Study Definition

Study end for a given subject will be marked following the r trieval of all Week 24 treatment assessments collected for the subject in the study and resolution of any complications from serious TEAEs. The study enrollment will not end until either the time that StrataGraft skin tissue is commercially available or the time that the Sponsor terminates the study, whichever occurs first. All subjects will be followed until th y complete their participation as described by this protocol.

6.2. Number of Subjects

Approximately 100 subjects will be scr ened and treated with StrataGraft skin tissue (enrolled into the study) until StrataGraft skin tissue is commercially available or until the Sponsor closes the study.

6.3. Treatment Assignment

Subjects who meet all inclusion criteria will receive StrataGraft skin tissue treatment. Subjects are considered enrolled into the study once they have StrataGraft skin tissue treatment applied to a burn site. Subjects will receive 1 application of StrataGraft skin tissue(s) to no more than 3 burn sites with no more than 20 StrataGraft skin tissues applied to the burn sites and a total study treatment area of no more than approximately 2000 cm^2.

6.4. Dose Adjustment Criteria

No dose adjustment will be made during this study.

6.5. Provisions for Remote Assessment Methods

For publicly stated emergency situations where there are extenuating circumstances that prohibit physical visits to the clinical site or when the safety of subjects may be compromised by physical visits to the site, provisions for remote assessments have been addressed.

For publicly stated emergency situations, the visit windows can be expanded as follows.

Weeks 1 and 2	± 5 days
Week 4	± 12 days
Weeks 8, 12, 24	± 14 days

Refer to the Manual of Procedures for a list of those assessments; remote collection of certain clinical assessments may be allowed.

6.6. Criteria for Study Stopping

Subject enrollment will be stopped if any of the following SAEs occur:

- Necrotizing soft tissue infection of th study wound attributed to StrataGraft skin tissue
- Severe acute hypersensitivity reaction attributed to StrataGraft skin tissue
- Death attributed to StrataGraft skin tissue

In the event that one of the listed SAEs occurs, the FDA and the local institutional review board (IRB) will be notified according to the decision tree for reporting SAEs as presented in the Manual of Procedures. The Medical Monitor will review the safety data associated with the adverse reaction with the clinical investigator and generate a summary narrative. The Medical Monitor, the Global Safety Lead, and the Clinical Trial Lead will conduct a comprehensive review of the safety data that will be submitted to the FDA prior to resumption of subject enrollment.

An independent adhoc Safety Committee made up of DSMB members familiar with other StrataGraft studies will be on stand-by to serve as external adjudicators in the event that any of the prior listed SAEs occurs and study enrollment is halted. The Safety Committee working with the Medical Monitor, the Global Safety Lead and the Clinical Trial Lead will determine if and when the study may be restarted.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Subject-specific criteria:

1. Men and women aged ≥ 18 years.
2. Written informed consent.
3. Sufficient healthy skin identified and designated as a donor site in the event that the StrataGraft treatment site requires autografting.
4. 3% up to <50%TBSA of partial +/- full thickness thermal burns

Treatment site-specific criteria:

5. Thermal burn(s) with intact dermal elements for which excision and autografting are clinically indicated
6. Total treatment areas no more than approximately 2000 cm^2 and total tissues no more than 20 tissues. Total burn may consist of no more than 3 noncontiguous burn sites
7. First excision and grafting of study treatment sites
8. Thermal burn(s) on the torso, upper extremities, and lower extremities

7.2. Subject Exclusion Criteria

Subject-specific criteria:

1. Pregnant women
2. Prisoners
3. Subjects receiving systemic immunosuppressive therapy at the time of injury
4. Subjects with a known history of malignancy
5. Pre-admission insulin-dependent diabetic subjects
6. Subjects with concurrent conditions that in the opinion of the investigator may compromise subject safety or study objectives
7. Expected survival of less than 3 months
8. Participation in an interventional study of an investigational device, pharmaceutical, or biologic drug within 90 days prior to enrollment

   (Note: Participants in nutritional or non-interventional observational studies where no investigational product or device is given or administered will not be excluded.)

Treatment site-specific criteria:

9. Full-thickness burns
10. Chronic wounds
11. The face, head, neck, hands, feet, digits, buttocks, perineum/genitals, and areas over joints

12. Treatment sites immediately adjacent to unexcised eschar
13. Clinical or laboratory determination of infection at the anticipated treatment sites at time of StrataGraft placement

7.3. Subject 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 abated or is judged as clinically stable by the Investigator.

A subject's participation may be discontinued at any time at the discretion of the Investigator if the subject is uncooperative, is noncompliant, or the Investigator feels that it is in the subject's best interest to be withdrawn from the study. 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.

In the event that a subject withdraws consent to participate in the study, the verbatim reason for withdrawal will be documented in the electronic case report form (eCRF). The subject will be asked to complete the current study evaluations but will be instructed that they are under no obligation to complete the study and are free to decline. The subject will be informed that they may be recontacted in the future by the study staff. At the time of withdrawal, a request for permission to review the subject's medical records at the 24-week time point will be made to check their status and for completion of study reporting forms. If the subject agrees to allow review of their medical records, they will sign a new Health Insurance Portability and Accountability Act authorization. Data collected under informed consent will be retained and included in the data analysis. If the subj ct indicates that their collected samples may no longer be used for the study, all retained unprocessed samples being held for analysis will be destroyed. However, archival samples that were collected per required agency regulations will be retained as required by regulations.

All subjects who discontinue from the study for any reason will be requested to provide contact information for the purpose of participation in a long-term follow up Registry Study. Subjects with closed wounds who complete the study will also have the opportunity to participate in the Registry Study and the consent form will be offered at the confirmation of healing visit. For those subjects whose wounds do not heal, they too would be offered the opportunity to participate in the Registry Study and the consent form will be offered during the study period.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Treatment

The study treatment is described in Table 3.

Table 3: Investigational Product

Product Name:	StrataGraft skin tissue
Dosage Form/Physical Description:	StrataGraft skin tissue is an off-white rectangular sheet of approximately 100 cm^2 (approximately 8 cm by 12.5 cm), consisting of a viable, bioengineered, regenerative skin construct derived from human keratinocytes grown on gelled collagen containing human dermal fibroblas s. StrataGraft skin tissue is stored at -70°C to -90°C until thawed for use. The hold solution that must be used with the StrataGraft skin tissue must be stored at 2° to 8°C until required for surgery.
Dosage	One application of sheets of no more than 20 StrataGraft skin tissues and applied to no more than 3 noncontiguous burn sites and applied to no more than approximately 2000 cm^2 total burn area to wounds with intact dermal elements
Route of Administration	StrataGraft skin tissue is applied topically to thermal burns 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.
Manufacturer	Stratatech, a Mallinckrodt Company

8.2. Concomitant Medications

All concomitant medications, including the use of antibiotics, must be recorded in the eCRF after the consent form is signed and throughout the study period. Systemic and topical antibiotics/antimicrobials may be used at the discretion of the clinical investigator with the exception of sulfamylon and silver-containing antimicrobials and silver-containing dressings. The use of sulfamylon and silver containing/releasing antimicrobials and dressings is not recommended as they are thought to interfere with the viability of the living cells in StrataGraft skin tissue. Prior to StrataGraft skin tissue placement, chlorhexidine can be applied to burn sites for wound preparation but must be thoroughly rinsed off prior to StrataGraft placement. After

StrataGraft skin tissue placement, further use of this antiseptic on the StrataGraft treatment site is also not recommended. Use of any of the aforementioned antiseptics at the discretion of the Principal Investigator, after StrataGraft skin tissue placement, would not be considered a protocol deviation. Additionally, investigational agents may not be used for the duration of study period. All other concomitant medications are unrestricted. Intravenous fluids generally used to maintain hydration and general anesthetic given during surgery need not be captured as concomitant medications.

8.3. Concomitant Procedures

Any concomitant procedure (including transfusions, use of xenogenic or allogeneic products, negative pressure wound therapy, etc.) must be recorded in the eCRF after the consent form is signed and throughout the duration of the study.

8.4. Randomization and Blinding

This study is designed as an open-label, single arm study in whi h all subjects receive StrataGraft skin tissue and all other burn wounds will be treat d per institutional SoC. No randomization will be conducted, and no blinding is required for the study.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Treatment

StrataGraft® skin tissue

9.2. Study Treatment Packaging and Labeling

See Investigator's Brochure

9.3. Study Treatment Storage

StrataGraft skin tissue is stored in a freezer at -70°C to -90°C.

9.4. Study Treatment Preparation

See Manual of Procedures: Patient Kit Receipt and StrataGraft Skin Tissue Thaw Instructions

9.5. Study Administration

Once the designated study site(s) have been excised and the subject is determined to meet all eligibility criteria, StrataGraft skin tissue will be meshed up to 1:1 and secured to the wound with sutures, staples, or tissue adhesives and then dressed with a non-adherent, porous dressing. Secondary dressings will be applied that are designed to maintain a moist wound environment and protect tissue from maceration and external contamination.

Silver-containing dressings are not recommended for use in this study. No adhesive dressing, tape, or adhesive strips, may be applied directly on the StrataGraft skin tissue-covered site or its periphery during the study period. Prior to StrataGraft skin tissue placement, chlorhexidine can be applied to burn sites for wound preparation but must be thoroughly rinsed off before StrataGraft placement. After StrataGraft skin tissue placement, further use of this antiseptic is not recommended.

It is not expected that StrataGraft skin tissue will incorporate into the wound bed due to vascular ingrowth as is seen with autologous skin grafts. It is anticipated that maximal benefit from treatment with StrataGraft skin tissue would come after maintenance of contact with the clean wound bed for as long as possible. Therefore, it is important to be careful during dressing changes during the first few weeks following placement.

Week 1: The non-adherent porous contact layer dressing should remain anchored in place for at least 3 days in order to prevent dislodging of the StrataGraft skin tissue. This non-adherent layer may or may not be replaced at the discretion of the Investigator. The frequency of changes of the secondary dressings is at the discretion of the Investigator paying attention to the precautions listed below.

Weeks 2 to 3: The contact layer dressing may be removed with care not to dislodge any remaining adherent StrataGraft skin tissue. Replacement of a nonadherent contact layer is recommended. All secondary dressings and frequency of changes are at the discretion of the Investigator paying attention to the precautions listed below. The healing epidermis beneath StrataGraft skin tissue may result in small areas of drying and lifting of StrataGraft changing the appearance to one that may be described as shabby or flaky. Over time, the dried StrataGraft skin

tissue will flake off during daily washing and wound care per institutional standard of care as the new, healthy epidermis expands beneath it. The healing wound still requires protection from shear forces as the new skin matures.

Week 4 through remainder of study: All dressings will be changed per institutional SoC until healing, or as long as deemed clinically necessary by the Investigator.

9.6. Study Treatment Handling and Disposal

See Manual of Procedures: Patient Kit Receipt Instructions, Chain of Custody Document Examples, and Record of Shipment Document Examples.

10. ASSESSMENT OF OTHER PRE-SPECIFIED ENDPOINTS

Wound closure

Complete wound closure is defined as 100% skin re-epithelialization in the absence of drainage. Successful wound closure in this study requires that complete wound closure is achieved without autograft placement and is confirmed at least 2 weeks following the initial observation of complete closure. The clinical investigator will evaluate treatment site(s), assess the proportion of the treated wound closed, complete wound closure, and confirmation of complete wound closure either by direct clinician observation or by subject-provided photo-documentation per Schedule of Assessments (Section 6.1.1).

Photo-documentation

Photographs will be taken by the clinician to supplement clinical assessment of percentage epithelialization, complete wound closure, confirmed wound closure, durable wound closure and the POSAS assessments (eg, appearance and cosmesis) of the treatment sites. Photographs taken and submitted by the subject (or other person designated by the subject) may be used for evidence of wound characteristics if a visit is missed or for a unscheduled visit. Photo-documentation is submitted by the subject beginning at discharge then weekly until Week 12 and then every other week until Week 24. These subject-submitted photos are only possible if the Principal Investigator gives approval for the subject to take off their dressings at home. In the event the dressings are not allowed to be changed at home, no subject photos will be expected or required. Photos submitted during weeks when there are no in-person visits would serve as an allowable proxy for observing wound characteristics. If a subject's wound is noted to be closed for the first time via a submitted photo, that photo should trigger the scheduling of a visit 2 weeks later for confirmation of wound healing. See Manual of Procedures for specific instructions regarding the methodology for obtaining photographs.

10.1. Other Endpoints

Assessments will be documented to determine other endpoints:

- Proportion of subjects with confirmed wound closure without autograft placement (ie, complete re-epithelialization without drainage and subsequently verified with confirmation assessment) on or before Week 12 and supported by photo-documentation
- Proportion of subjects with confirmed wound closure without autograft (verified with confirmation assessment) at each visit and supported by photo-documentation
- Proportion of subjects without autografting who maintain durable wound closure by Week 24
- Time to confirmed wound closure without autografting (verified with confirmation assessment)
- Treatment site skin quality data: The total observed POSAS by clinician and by subject. Per site descriptive statistics will be presented separately for clinician and subject values for each of the individual POSAS items and the total POSAS score,

represented as the mean score across all treatment sites and supported by photo documentation

- Number (%) of subjects with wound infection-related events

10.2. Exploratory Endpoints

HCRU Assessments

Assessments will be documented for the following as exploratory endpoints:

- Location of care for StrataGraft application (eg, inpatient hospital, outpatient/ambulatory hospital, clinic, etc.)
- Treatments used for all other burn areas following excision and %TBSA treated with each (other than StrataGraft treatment sites)
- Number of OR procedures required for burn treatment: excisions, application of StrataGraft tissue and all other grafting procedures, including autografts and xenografts
- Duration of each OR procedure
- Length of hospital stay
- Prescription drugs given at discharge from the hospital for wound-related events including pain control, itch, psychotropics, and antibiotics
- Re-admission within 30 days after discharge
- Whether a re-admission is planned
- Length of hospital stay of e-admission

10.3. Subgroup Analyses

Subgroup Assessments

Subgroup analyses will include the following categories:

- Sex
- Race (white, non-white)
- Ethnicity (Hispanic, non-Hispanic)
- Age (< 65, ≥ 65)
- Size of area treated with StrataGraft (≤ 500 cm^2, > 500 cm^2)
- Overall TBSA of wound burden (burn areas plus donor site area; < median, ≥ median)

11. OTHER ASSESSMENTS

A subset of 10 subjects with closed wounds (from subjects who have achieved wound closure, across all the clinical sites) will be separately consented to have a punch biopsy (measuring 3 mm) taken from the center of the healed burn wound, and another punch biopsy measuring 3 mm taken from non-burned healthy skin. A histological evaluation of both samples will be done to analyze and contrast the skin architecture in the healed burn wound with healthy skin. The biopsy will occur at the study visit Week 12, regardless of when wound closure occurs.

Wound assessments will include measurements for average depth, length, and width for calculations of area and percent epithelialization. Wound assessments will be facilitated by photographs taken by the subject and/or taken by the clinical study site staff at study visits throughout the study.

12. SAFETY ASSESSMENT

Safety will be monitored from the time of subject signing consent to participate in the study and includes: TEAEs, treatment-emergent SAEs, local wound infections, systemic infections, vital signs, and deaths throughout the study duration. In addition to the collection of common clinical study safety data, blood samples (blood plasma and leucocytes) will be collected to comply with the archival xenotransplantation FDA requirements.

12.1. Primary Safety Endpoint

The primary objective of this study is to demonstrate the safety of a single application of StrataGraft skin tissue in the post excision treatment of thermally induced DPT burns that contain intact dermal elements. The primary safety endpoint is the count and percentage of subjects with TEAEs.

Primary Outcome Measure:

Title:

Number of subjects with TEAEs

Description:

Total count of participants observed with TEAEs during the study

Timeframe:

Approximately 24 weeks

12.2. Safety Parameters Specific to Therapeutic Category

12.2.1. Incidence of infection

Local wound 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^{o}C) and/or elevated white blood cell count.

Study treatment sites will be examined by the investigator for signs and symptoms of infection at every study visit. Cultures of the treatment sites may be obtained for microbiological evaluation at the discretion of the clinical investigator or per institutional SoC at any time during treatment. The clinical investigator will evaluate the wound culture results for clinical significance. Infections and their treatment must be documented in the eCRF with notation of StrataGraft-treated site or “Other” (ie, SoC treatment).

12.2.2. Archival plasma and leukocyte samples

In accordance with current xenotransplantation FDA Guidance, an archival blood sample will be collected at Day 1 (Baseline) prior to StrataGraft skin tissue placement and retained. For further detail, see Manual of Procedures, Subject Plasma and Leukocyte Archival.

12.2.3. Immunology

Blood collection for PRA testing (HLA I and II) will be conducted at Day 1 (Baseline), Week 4, and Week 12.

12.2.4. Regrafting and Delayed Wound Healing

In the event that a StrataGraft-treated area needs to be regrafted with either an autograft or a xenograft after prior treatment with StrataGraft skin tissue, the event would not be marked as an AE, but rather as a failure to close. In the event that there is an accompanying wound degradation event occurring simultaneously such as infectio that results in delayed wound healing, the delayed wound healing secondary to the ongoing inf ction can be listed as an AE or SAE as applicable. If that infective process eventually w rrants regrafting, the regrafting should still be marked as a failure to close and not an AE.

12.3. Standard Safety Parameters

12.3.1. Demographic/Social/Medical History

Past medical history, social, and acute medical history will be collected at Screening. Medical history will be reviewed for eligibility for enrollment into the study as described in the inclusion criteria.

12.3.2. Vital Signs

Vital signs (blood pressure, p lse rate, temperature) will be measured at each scheduled study time point. The change from baseline will be calculated for each study time point for clinical safety analyses.

12.3.3. Weight and Height

Weight and height will be measured at Screening.

12.3.4. Physical Examination

The limited Physical Examination will be conducted at Screening to include evaluation of lungs, heart, abdomen, and extremities. The findings of the physical examination will be recorded on the eCRF.

12.3.5. Laboratory Assessments

Laboratory safety parameters will be evaluated for clinically significant changes within this subject population at Baseline, defined study intervals, and as deemed appropriate by the clinician according to the institutional SoC in the evaluation of study subjects.

12.3.5.1. Hematology

Hematology evaluations will include hemoglobin, platelets, red blood cell count and white blood cell count with differential.

12.3.5.2. Blood Chemistry

Blood chemistry assessments will include alanine transaminase, aspartate transaminase, and bilirubin, glucose, electrolytes, and creatinine.

12.3.5.3. Immunology Assessments

Immunological evaluations will include PRA with HLA class I and II screening and testing for allelic reactivity.

12.3.5.4. Pregnancy Testing

A serum pregnancy test for women of child-bearing potential will be performed at Screening using the local laboratory. Should a pregnancy be confirmed after placement of StrataGraft, the pregnancy will be reported as a special event (ie, not an AE). Since StrataGraft skin tissue is a single application, the subject will continue with all scheduled study evaluations. Pregnant subjects will be followed until post-partum and the outcome of the pregnancy will be reported.

12.4. Adverse Events and Serious Adverse Events

Definition of Adverse Events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including Baseline or washout periods, even if no study treatment has been administered.

All AEs that occur after any subject has signed the consent form and the AEs occurring during treatment must be recorded on forms provided by the Sponsor, whether or not they are related to the study.

Definition of SAE

An SAE is an AE occurring during any part of the study period (ie, Baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following:

- Results in death; all AEs with an outcome of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to the Sponsor or designee, or state “not available.”
- It is immediately life-threatening
- It requires inpatient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

12.5. Intensity of Adverse Event

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity of an AE, whereas seriousness is defined by the criteria under Section 12.4. An AE of severe intensity may not always be considered an SAE.

12.6. Relationship to Study Drug

An Investigator who is licensed to practice medicine must make the determination of relationship to the investigational product for each AE (unrelated, possibly related or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable", the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

12.7. Other Adverse Event

The Drug Safety Physician and, if applicable, the Clinical Study Team Physician will identify other adverse event(s) during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance will be collected as adverse events of special interest, ie, events other than SAEs and those AEs leading to discontinuation of the subject from the study). For each adverse event of special interest, a narrative may be written and included in the clinical study report.

12.8. Pregnancy Events

Should a pregnancy occur, it must be reported and recorded on the Sponsor's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality/birth defects) must be recorded on the eCRF, even if the subject is discontinued from the study. Elective abortions without complications are not considered an AE and are not reported as an AE.

All reports of congenital abnormalities/birth defects, spontaneous miscarriages, and serious complications due to pregnancy should be reported as SAEs.

In this study, subjects will not be discontinued from the study unless the subject elects to withdraw consent.

12.9. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse rate need not be reported as AEs. However, abnormal values that constitute an SAE, are associated with an SAE, or lead to discontinuation of administration of study treatment must be reported and recorded as an AE. Information about AEs will be collected from the signing of consent form until the end of the study. All SAE information will be collected from the signing of consent form and throughout the study follow-up period. The AE terms should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.

12.10. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from the signing of consent form until following the end of treatment exposure. All SAEs must be reported to Sponsor within 1 business day of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax to the Sponsor.

Additional follow-up information, if required or available, should all be faxed to the Sponsor within 1 business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

The Sponsor is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, treatment-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB or IEC of all SAEs.

13. STATISTICS

13.1. Sample Size Determinations

No sample size determination was made for this study, as this is 1 treatment group, non-randomized study designed to accumulate supplemental safety and efficacy data for the use of StrataGraft for the treatment of DPT wounds with intact dermal elements. This study will enroll approximately 100 subjects from up to 18 clinical study centers that previously participated in the prior Phase 3 study.

13.2. Analysis Populations

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

The modified intention-to-treat (mITT) population will include all subjects who enrolled and received StrataGraft skin tissue. The safety and efficacy analyses will be based on the mITT population.

13.3. Statistical Analysis

This section provides a general summary of the statistical methods to be used in analyzing study data. A more detailed statistical analysis plan will be provided in a separate document that will be finalized prior to database lock.

Descriptive statistics for continuous variables will include the mean, median, standard deviation, minimum value, and maximum value. Categorical data will be summarized by counts and percentages.

Assessments of photographs of burn sites will be used as confirmatory evidence of durable closure in cases of absence of an in-person visit and for weeks where an in-person visit is not scheduled.

All data documented in the eCRFs and laboratory test results, including repeated and unscheduled assessments, will be presented in data listings.

13.3.1. Primary Safety Endpoint Analysis

The primary endpoint analysis will be count and percent of subjects with TEAEs. This endpoint will be analyzed based on the mITT population.

13.3.2. Other Pre-specified Endpoint Analyses

For this study, confirmed wound closure is defined as meeting wound determinations at 2 visits:

1. First, a visit at which the clinician determined complete (100%) re-epithelialization without drainage
2. Second, an assessment at a subsequent visit that is at least 2 weeks later than the first visit and wound closure was confirmed (ie, determined again) to be completely closed

Durable wound closure is achieved when a wound is observed as remaining closed at least 3 months after complete wound closure.

The clinician may determine confirmed wound closure and durable closure either by directly observing the wound or by assessing appropriate photo-documentation that will be provided electronically by the subject weekly for the first 12 weeks and then provided every other week through to Week 24. The following endpoints will be analyzed with descriptive statistics with 95% confidence intervals:

- Proportion of subjects with confirmed wound closure without autograft placement (ie, complete re-epithelialization without drainage and subsequently verified with confirmation assessment) on or before Week 12 and supported by photo-documentation
- Proportion of subjects with confirmed wound closure without autograft (verified with confirmation assessment) at each visit and supported by photo-documentation
- Proportion of subjects without autografting who maintain durable wound closure by Week 24
- Time to confirmed wound closure without autografting (verified with confirmation assessment)
- Treatment site skin quality data: The total observed POSAS by clinician and by subject. Per site descriptive statistics will be presented separately for clinician and subject values for each of the individual POSAS items and the total POSAS score, represented as the mean score across all treatment sites and supported by photo-documentation
- Number (%) of subjects with wound infection-related events

The time to first confirmed wound closure (verified with confirmation assessment) will be analyzed by the Kaplan-Meier estimation method. The period for this analysis is calculated as (the date of having the first event the date of Day 1 + 1). Subjects not having any event during the study will have their time censored at the last available date in the study. Kaplan-Meier estimates by StrataGraft treatment area with confirmed wound closure will be presented for the following categories: ≤ 500 cm^2, > 500 cm^2.

13.3.3. Exploratory Efficacy Endpoints

Results from all HCRU parameters as exploratory efficacy endpoints will be summarized with descriptive statistics by visit:

- Location of care for StrataGraft application (eg, inpatient hospital, outpatient/ambulatory hospital, clinic, etc.)
- Treatments used for all other burn areas following excision and %TBSA treated with each (other than StrataGraft treatment sites)
- Number of OR procedures required for burn treatment: excisions, application of StrataGraft tissue and all other grafting procedures, including autografts, allografts, and xenografts
- Duration of each OR procedure
- Length of hospital stay

- Prescription drugs given at discharge from the hospital for wound-related events including pain control, itch, psychotropics, and antibiotics
- Re-admission within 30 days after discharge
- Whether re-admission is planned
- Length of hospital stay of re-admission

13.3.4. Subgroup Analyses

The complete wound closure and TEAE endpoints will be summarized by the following demographic and baseline characteristics:

- Race (white, non-white)
- Ethnicity (Hispanic, non-Hispanic)
- Age (<65, ≥ 65)
- Sex (Male, Female)
- StrataGraft size of the area (≤ 500 cm^2, > 500 cm^2)
- Overall TBSA of wound burden defined as burns plus donor site area (< median, ≥ median)

13.3.5. Multiple Comparison Testing Methods

Adjustment for multiplicity does not apply to nalysis of the endpoints for this study.

13.3.6. Interim Analyses

No statistical interim analyses for fficacy are planned for this study.

13.3.7. Safety Analysis

The primary safety endpoint analysis will be count and percent of subjects with TEAEs and will be based on mITT population.

No formal hypothesis testing will be performed for any safety variables. All safety variables will be summarized with descriptive statistics.

Adverse Events

The TEAE is defined as those adverse events with onset date and time after the first placement of study product or those events in which the onset date and time are before the first placement of study product but worsened after the first placement of study product. Coding of adverse events will be performed using the Medical Dictionary for Regulatory Activities classification system.

The number (%) of TEAE of subjects who experienced at least 1 TEAE will be summarized by system organ class and by preferred term. The TEAEs will also be summarized by maximum severity and by strongest relationship to StrataGraft skin tissue. The TEAEs on study treatment sites (StrataGraft skin tissue-treated sites) and other nonstudy treatment (SoC-treated sites) will be summarized by system organ class and by preferred term; SAE will be tabulated and listed in a manner similar to TEAE.

Infection

The incidence of infection of the study treatment sites will be presented.

Vital Signs

Vital signs (blood pressure, pulse rate, temperature) will be calculated and presented at each scheduled time point, as will the change from Baseline.

Safety Laboratory Parameters

Safety laboratory tests (including creatinine and complete blood count with differential) will be calculated and presented at each scheduled time point, as will the change from Baseline.

Safety laboratory test results will be categorized and presented as "Low," "Normal" and "High", as defined by the sites' laboratory normal range. Additionally, shift tables will be presented summarizing changes from normal to out-of-normal range.

13.3.8. Handling of Missing Data

No imputation for missing values will be conducted. All obs rved values (ie, excluding missing values for visit) will be used for the analyses.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the investigator.

During the study, a monitor from the Sponsor or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, medical records).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

14.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Council for Harmonisation, and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

14.3. Monitoring Boards

The Principal Investigator must obtain IRB approval for the investigation. All IRB approvals, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

Additionally, an independent adhoc Safety Committee will ensure adequate protection of the safety of subjects. The Committee's objectives, composition, and operational details of its activities will be defined in the Safety Committee Charter.

In the event that an SAE occurs such that stopping the study is considered, the local IRB will be notified as presented in the Manual of Procedures.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The investigator must submit written approval to the Sponsor before he or she may enroll any subject into the study. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. Any amendment made to this protocol must be reviewed and approved by the IRB or IEC.

The Principal Investigator is also responsible for providing the IRB with reports as local regulations require, including any reported serious adverse treatment reactions arising from any other study conducted with the investigational product. The Sponsor will provide this information to the Principal Investigator.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that are consistent with ICH GCP, which has its ethical foundation in the Declaration of Helsinki and are consistent with applicable regulatory requirements.

16.3. Written Informed Consent

The Principal Investigator(s) at each study site will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

Consent must also be obtained for direct contact by Sponsor for the post study safety registry during the study period.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the study treatment storage area, study treatment stocks, study treatment accountability records, subject medical records and study source documents, and other records relative to study conduct.

17.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18. LIST OF REFERENCES

1. American Burn Association. National Burn Repository 2017 Report of Data from 2008-2017. Chicago, IL: American Burn Association, Dataset Version 13.0.
2. Bloom ET. January 13, 2000. Xenotransplantation Subcommittee. Division of Cellular and Gene Therapies, Office of Therapeutics Research and Review, FDA/CBER.
3. Burn Incidence and Treatment in the United States: 2016; 2016. accessed June 4, 2020. http://ameriburn.org/who-we-are/media/burn-incidence-fact-sheet/
4. FDA. Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans. December 2016.
5. Herndon DN, Barrow RE, Rutan RL, Rutan TC, Desai MH, Abston S. A comparison of conservative versus early excision therapies in severely burned patients. Ann Surg 1989; 209(5):547-52.
6. Muller MJ, Herndon DN. The challenge of burns. Lancet 1994;343:216–20.
7. Munster AM, Smith-Meek M, Sharkey P. The effect of early surgical intervention on mortality and cost-effectiveness in burn care, 1978-91. Burns 1994; 20:61–4.

APPENDIX 1 PROTOCOL AMENDMENT HISTORY

Amendment 1 includes the details for all changes as detailed in this appendix: provisions for publicly stated emergencies, DSMB safety monitoring has been replaced with monitoring by Sponsor Safety Committee, safety laboratory assessments added, and clarification added for wound assessments, for collection of photographs, and for collection of data for prescription medications plus other minor changes and administrative changes.

Protocol Section/Issue/Rationale for Change	**Removed Text Displayed in Strikethrough Font**	**New Text Bolded**
Section 1 Synopsis Other Endpoints • Proportion of subjects with complete wound closure without autograft (verified with confirmation assessment) on- or before Week 12 and supported by photodocumentation • Proportion of subjects with complete wound closure without autograft (verified with confirmation assessment) at each visit and supported by photodocumentation • Proportion of subjects maintaining durable wound closure by Week 24 • Time to complete wound closure without autograft (verified with confirmation assessment) • Skin quality and cosmesis of treated sites assessed by the subject and	Section 1 Synopsis Other Endpoints • Proportion of subjects with ~~comple e~~ wound closure without autograft ~~(~~verified with confirmation assessment) on~~-~~ or befor Week 12 and supported by photodocumentation • Proportion of subjects with ~~complete~~ wound closure without autograft (verified with confirmation assessment) at each visit and supported by photodocumentation • Proportion of subjects ~~maintaining~~ durable wound closure by Week 24 • Time to ~~complete~~ wound closure without autograft	Section 1 Synopsis Other Endpoints • Proportion of subjects with **confirmed** wound closure without autograft **placement (ie complete re-epithelialization without drainage and subsequently** verified with confirmation assessment) on or before Week 12 and supported by photo-documentation • Proportion of subjects with **confirmed** wound closure without autograft (verified with confirmation assessment) at each visit and supported by photo-documentation • Proportion of subjects **without autografting who maintain**

Protocol Section/Issue/Rationale for Change	Removed Text Displayed in Strikethrough Font	New Text Bolded
observer using the scar assessment scale (POSAS) and supported by photo documentation • Number of subjects with wound-infection related events	(verified with confirmation assessment) • ~~Skin quality and cosmesis of treated sites assessed by the subject and observer using the scar assessment scale (POSAS)~~ and supported by photo documentation • Number of subjects with wound-infection related e nts	durable wound closure by Week 24 • Time to **confirmed** wound closure without autograft**ing** (verified with confirmation assessment) • **Treatment site skin quality data: The total observed POSAS by clinician and by subject. Per site descriptive statistics will be presented separately for clinician and subject values for each of the individual POSAS items and the total POSAS score, represented as the mean score across all treatment sites** and supported by photo documentation • Number **(%)** of subjects with wound-infection related events
Methodology: The data generally will be summarized with descriptive statistics. The Kaplan-Meier estimate will be performed to determine time to complete wound closure.	**Methodology:** The data generally will be summarized with descriptive statistics. The Kaplan-Meier estimate will be performed to determine time to ~~complete~~ wound closure	**Methodology:** The data generally will be summarized with descriptive statistics. The Kaplan-Meier estimate will be performed to determine time to **confirmed** wound closure

Protocol Section/Issue/Rationale for Change	Removed Text Displayed in Strikethrough Font	New Text Bolded
Statistical Methods: The Kaplan-Meier estimate will be computed to determine the median time to complete wound closure without autograft placement (verified with confirmation assessment). Section 5.2 Other Objectives Other Pre-specified Objective(s)/ Endpoint(s) Other Endpoints • Proportion of subjects with complete wound closure without autograft (verified with confirmation assessment) on- or before Week 12 and supported by photodocumentation • Proportion of subjects with complete wound closure without autograft (verified with confirmation assessment) at each visit and supported by photodocumentation • Proportion of subjects maintaining durable wound closure by Week 24	**Statistical Methods:** The Kaplan-Meier estimate will be computed to determine the median time to ~~complete~~ wound closure without autograft placement (verified with confirmation assessment). Section 5.2 Other Obje tives Other Pre-specified Obj ctive(s)/ Endpoint(s) Other Endpoints • Propo tion of subjects with ~~complete~~ wound closure without autograft (verified with confirmation assessment) on- or before Week 12 and supported by photodocumentation • Proportion of subjects with ~~complete~~ wound closure without autograft (verified with confirmation assessment) at each visit and supported by photodocumentation	**Statistical Methods:** The Kaplan-Meier estimate will be computed to determine the median time to **confirmed** wound closure without autograft placement (verified with confirmation assessment). Section 5.2 Other Objectives Other Pre-specified Objective(s)/ Endpoint(s) Other Endpoints • Proportion of subjects with **confirmed** wound closure without autograft **placement (ie complete re-epithelialization without drainage and subsequently** verified with confirmation assessment) on or before Week 12 and supported by photo-documentation • Proportion of subjects with **confirmed** wound closure without autograft (verified with confirmation assessment) at each visit and supported by photo-documentation

Protocol Section/Issue/Rationale for Change	Removed Text Displayed in Strikethrough Font	New Text Bolded
• Time to complete wound closure without autograft (verified with confirmation assessment) • Skin quality and cosmesis of treated sites assessed by the subject and observer using the scar assessment scale (POSAS) and supported by photo documentation • Number of subjects with wound-infection related events	• Proportion of subjects ~~maintaining~~ durable wound closure by Week 24 • Time to ~~complete~~ wound closure without autograft (verified with confirmation assessment) • ~~Skin quality and cosmesis of treated sites assessed by the subject and observer using the scar assessment scale (POSAS)~~ and suppor ed by photo documentation • Number of subjects with wo nd-infection related events	• Proportion of subjects **without autografting who maintain**durable wound closure by Week 24 • Time to **confirmed** wound closure without autograft**ing** (verified with confirmation assessment) • **Treatment site skin quality data: The total observed POSAS by clinician and by subject. Per site descriptive statistics will be presented separately for clinician and subject values for each of the individual POSAS items and the total POSAS score, represented as the mean score across all treatment sites** and supported by photo documentation • Number **(%)** of subjects with wound-infection related events Section 6.1 Overall Study Design Other endpoints include:

Protocol Section/Issue/Rationale for Change	Removed Text Displayed in Strikethrough Font	New Text Bolded
Section 6.1 Overall Study Design Other endpoints include: • The proportion of StrataGraft skin tissue-treated wound area with complete wound closure without autograft placement (i.e. complete re-epithelialization without drainage and subsequently verified by confirmation assessment) on- or before Week 12 and supported by photodocumentation. • The proportion of subjects with complete wound closure without autograft placement (verified with confirmation assessment) at each visit. • The proportion of subjects achieving and maintaining durable wound closure by Week 24. Durable wound closure is achieved when a wound is observed as remaining closed at least 3 months after complete wound closure. • Time to complete wound closure without autograft	Section 6.1 Overall Study Design Other endpoints include: • The proportion of StrataGraft skin tissue-treated wound area with ~~complete~~ wound closure without autograft placement (i.e. complete re-epithelialization without drainage and subsequently verified by confirmation assessment) on~~-~~ or before Week 12 and supported by photod cumentation. • The proportion of subjects with ~~complete~~ wound closure witho t autograft placement (verified with confirmation assessment) at each visit. • The proportion of subjects achieving and maintaining durable wound closure by Week 24. Durable wound closure is achieved when a wound is observed as remaining closed at least 3 months after complete wound closure. • Time to ~~complete~~ wound closure without autograft	• The proportion of StrataGraft skin tissue-treated wound area with **confirmed** wound closure without autograft placement (ie, complete re-epithelialization without drainage and subsequently verified by confirmation assessment) on or before Week 12 and supported by photodocumentation. • The proportion of subjects with **confirmed** wound closure without autograft placement (verified with confirmation assessment) at each visit **and supported by photo-documentation**. • The proportion of subjects **without autografting** achieving and maintaining durable wound closure by Week 24. Durable wound closure is achieved when a wound is observed as remaining closed at least 3 months after complete wound closure. • Time to **confirmed** wound closure without autograft placement (verified with

Protocol Section/Issue/Rationale for Change	Removed Text Displayed in Strikethrough Font	New Text Bolded
placement (verified with confirmation assessment). For in person visits, the investigator will assess the wound in person or alternatively assess a photo provided by the subject if the subject misses a visit. For the weeks in-between onsite visits, the subject will have a photo taken and send them to a photo repository beginning at discharge then weekly until Week 12 and then every other week until Week 24. These photos will also be assessed by the principal investigator. • …. • Number of subjects with wound-infection related events./ Section 10 Assessment of Other Pre-Specified Endpoints Wound closure Complete wound closure is defined as 100% skin re-epithelialization in the absence of drainage and without autograft placement./	placement (verified with confirmation assessment). For in person visits, the investigator will assess the wound in person or alternatively assess a photo provided by the subject if the subject misses a visit. For the weeks in-between onsite visits, the subject will have a ph to taken and send them to a photo repository beginning at discharge then weekly until Week 12 and then every other week until Week 24. These photos will also be assessed by the principal investigator. …. • Number of subjects with wound-infection related events./ Section 10 Assessment of Other Pre-Specified Endpoints Wound closure Complete wound closure is defined as 100% skin re-epithelialization in the absence of drainage ~~and without autograft placement./~~	confirmation assessment). For in person visits, the investigator will assess the wound in person or alternatively assess a photo provided by the subject if the subject misses a visit. For the weeks in-between onsite visits, the subject will have a photo taken and send them to a photo repository beginning at discharge then weekly until Week 12 and then every other week until Week 24. These photos will also be assessed by the principal investigator. • …. • Number of subjects **(%)** with wound-infection related events./

Protocol Section/Issue/Rationale for Change	Removed Text Displayed in Strikethrough Font	New Text Bolded
Section 10.1 Other Endpoints • Proportion of subjects with complete wound closure without autograft (verified with confirmation assessment) on- or before Week 12 and supported by photodocumentation • Proportion of subjects with complete wound closure without autograft (verified with confirmation assessment) at each visit and supported by photodocumentation • Proportion of subjects maintaining durable wound closure by Week 24 • Time to complete wound closure without autograft (verified with confirmation assessment) • Skin quality and cosmesis of treated sites assessed by the subject and observer using the scar assessment scale (POSAS) and supported by photo documentation • Number of subjects with wound-infection related events	Section 10.1 Other Endpoints • Proportion of subjects with ~~complete~~ wound closure without autograft ~~(~~verified with confirmation assessment) on~~-~~ or before Week 12 and supported by photodocumentation • Proportion of subjects with ~~complete~~ wound closure without autograft (verified with confirmation ass ssment) at each visit and supported by photodo umentation • Proportion of subjects ~~maintaining~~ durable wound closure by Week 24 • Time to ~~complete~~ wound closure without autograft (verified with confirmation assessment) • ~~Skin quality and cosmesis of treated sites assessed by the subject and observer using the scar assessment scale (POSAS)~~ and supported by photo documentation	Section 10.1 Other Endpoints • Proportion of subjects with **confirmed** wound closure without autograft **placement (ie complete re-epithelialization without drainage and subsequently** verified with confirmation assessment) on or before Week 12 and supported by photo-documentation • Proportion of subjects with **confirmed** wound closure without autograft (verified with confirmation assessment) at each visit and supported by photo-documentation • Proportion of subjects **without autografting who maintain** durable wound closure by Week 24 • Time to **confirmed** wound closure without autograft**ing** (verified with confirmation assessment) • **Treatment site skin quality data: The total observed POSAS by clinician and by subject. Per site descriptive**

Protocol Section/Issue/Rationale for Change	Removed Text Displayed in Strikethrough Font	New Text Bolded
	• Number of subjects with wound-infection related events	**statistics will be presented separately for clinician and subject values for each of the individual POSAS items and the total POSAS score, represented as the mean score across all treatment sites** and supported by photo documentation • Number **(%)** of subjects with wound-infection related events
Section 12.3.2 Other Pre-specified Endpoint Analyses For this study, confirmed wound closure is defined as meeting wound determinations at 2 visits: 8. First, a visit at which the clinician determined complete (100%) re-epithelialization without drainage and without autografting ….	Section ~~12~~.3.2 Other Pre-specified Endpoint Analyses For this study, confirmed wound closure is defined as meeting wound determinations at 2 visits: 9. First, a visit at which the clinician determined complete (100%) re-epithelialization without drainage ~~and without autografting~~	Section **13**.3.2 Other Pre-specified Endpoint Analyses For this study, confirmed wound closure is defined as meeting wound determinations at 2 visits: 10. First, a visit at which the clinician determined complete (100%) re-epithelialization without drainage ….. • **P**roportion of subjects with **confirmed** wound closure without autograft placement (ie complete re-epithelialization

Protocol Section/Issue/Rationale for Change	Removed Text Displayed in Strikethrough Font	New Text Bolded
• The proportion of subjects with wound closure without autograft placement (verified with confirmation assessment) at each study visit. • The proportion of subjects maintaining durable wound closure by Week 24 • Treatment site skin quality data: The total observed POSAS by clinician and by subject. Per-site descriptive statistics will be presented separately for clinician and subject values for each of the individual POSAS items and the total POSAS score at each time of assessment. • Number (%) of subjects with wound infection-related events	….. • ~~The~~ proportion of subjects with wound closure without autograft ~~(~~verified with confirmation assessment) ~~at each study visit~~ • ~~The~~ proportion of subjects ~~maintaining~~ durable wound closure by Week 24 • Treatment site sk n quality data: The tot l obs rved POSAS by clinician and by subject. Per-si e descriptive statistics will be pres nted separately for clinician and subject values for each of the individual POSAS items and the total POSAS score at each time of assessment. • Number of subjects with wound-infection related events	without drainage and subsequently verified with confirmation assessment) **on or before Week 12 and supported by photo-documentation** • **Proportion of subjects with confirmed wound closure without autograft (verified with confirmation assessment) at each visit and supported by photo-documentation** • Proportion of subjects **without autografting who maintain** durable wound closure by Week 24 • **Time to confirmed wound closure without autografting (verified with confirmation assessment)** • Treatment site skin quality data: The total observed POSAS by clinician and by subject**. Per site** descriptive statistics will be presented separately for clinician and subject values for each of the individual POSAS items and the total POSAS

Protocol Section/Issue/Rationale for Change	Removed Text Displayed in Strikethrough Font	New Text Bolded
Rationale: Complete wound closure can be achieved with the use of other grafts, including xenograft and autograft. Updated the endpoints to be consistent across all sections of the protocol.		score, represented as the mean score across all treatment sites **and supported by photo-documentation.** • Number **(%)** of subjects with wound-infection related events
Section 1 Synopsis Study Design Treatment will include a single application of up to 1:1 meshed StrataGraft skin tissue on DPT wound(s) totaling no more than approximately 1,000 square centimeters in area (no more than 3 study treatment thermal burn areas and no more than 10 StrataGraft tissues applied to the study treatment areas)./ Inclusion Criteria Inclusion Criterion #6 Total treatment area~~s~~ no more than approximately 1000 cm^2 and total tissues no	Section 1 Synopsis Study Design Treatment w ll include a single application of up to 1 1 meshed StrataGraft skin tissue on DPT wo nd(s) totaling no more than approximately ~~1,000~~ square centimeters in area (no more than 3 study treatment thermal burn areas and no more than ~~10~~ StrataGraft tissues applied to the study treatment areas)./ Inclusion Criteria Inclusion Criterion #6 Total treatment area~~s~~ no more than approximately ~~1000 cm~~^{2} and total tissues no	Section 1 Synopsis Study Design Treatment will include a single application of up to 1:1 meshed StrataGraft skin tissue on DPT wound(s) totaling no more than approximately **2000** square centimeters in area (no more than 3 study treatment thermal burn areas and no more than **20** StrataGraft tissues applied to the study treatment areas)./ Inclusion Criteria Inclusion Criterion #6 Total treatment area~~s~~ no more than approximately **2000** cm^2 and total tissues no

Protocol Section/Issue/Rationale for Change	**Removed Text Displayed in Strikethrough Font**	**New Text Bolded**
more than 10 tissues. Total burn may consist of no more than 3 noncontiguous burn sites./	more than ~~10~~ tissues. Total burn may consist of no more than 3 noncontiguous burn sites./	more than **20** tissues. Total burn may consist of no more than 3 noncontiguous burn sites./
Investigational Product, Dosage and Mode of Administration	Investigational Product, Dosage and Mode of Administration	Investigational Product, Dosage and Mode of Administration
StrataGraft skin tissue is applied once to no more than 3 noncontiguous burn sites, totaling a maximum study treatment area of no more than approximately 1000 cm^2, and using no more than 10 tissues./	StrataGraft skin tissue is applied once to no more than 3 noncontiguous burn sites, totaling a maximum study treatment area of no more than approximately ~~1000~~ cm^2, and using no more than ~~10~~ tissues./	StrataGraft skin tissue is applied once to no more than 3 noncontiguous burn sites, totaling a maximum study treatment area of no more than approximately **2000** cm^2, and using no more than **20** tissues./
Section 6.1 Overall Study Design	Section 6.1 Overa l Study Design	Section 6.1 Overall Study Design
Subjects may be assessed to have no more than 3 noncontiguous burn areas treated and receive no more than 10 tissues of StrataGraft skin tissue (for a total StrataGraft skin tissue treated area of no more than approximately 1,000 cm^2)./	Subjects may be assessed to have no more than 3 n ncontiguous burn areas treated and receive no more than ~~10~~ tissues of StrataGraft skin tissue (for a total StrataGraft skin tissue treated area of no more than approximately ~~1000~~ cm^2)./	Subjects may be assessed to have no more than 3 noncontiguous burn areas treated and receive no more than **20** tissues of StrataGraft skin tissue (for a total StrataGraft skin tissue treated area of no more than approximately **2000** cm^2)./
Section 6.3 Treatment Assignment	Section 6.3 Treatment Assignment	Section 6.3 Treatment Assignment
Subjects will receive 1 application of StrataGraft skin tissue(s) to no more than 3 burn sites with no more than 10 StrataGraft skin tissues applied to the burn sites and a	Subjects will receive 1 application of StrataGraft skin tissue(s) to no more than 3 burn sites with no more than ~~10~~ StrataGraft skin tissues applied to the burn sites and a	Subjects will receive 1 application of StrataGraft skin tissue(s) to no more than 3 burn sites with no more than **20** StrataGraft skin tissues applied to the burn sites and a

Protocol Section/Issue/Rationale for Change	**Removed Text Displayed in Strikethrough Font**	**New Text Bolded**
total study treatment area of no more than approximately 1000 cm^2./	total study treatment area of no more than approximately ~~1000~~ cm^2./	total study treatment area of no more than approximately **2000** cm^2./
Section 7 Selection and Withdrawal of Subjects	Section 7 Selection and Withdrawal of Subjects	Section 7 Selection and Withdrawal of Subjects
Inclusion Criterion #6	Inclusion Criterion #6	Inclusion Criterion #6
Total treatment area~~s~~ no more than approximately 1000 cm^2 and total tissues no more than 10 tissues. Total burn may consist of no more than 3 noncontiguous burn sites./	Total treatment area~~s~~ no more than approximately ~~1000~~ cm^2 and total ti sues no more than ~~10~~ tissues. Total burn may consist of no more than 3 noncontiguous burn sites./	Total treatment area~~s~~ no more than approximately **2000** cm^2 and total tissues no more than **20** tissues. Total burn may consist of no more than 3 noncontiguous burn sites./
Section 8.1 Description of Study Treatment	Section 8.1 D scription of Study Treatment	Section 8.1 Description of Study Treatment
Table 3: Investigational Product	Table 3: Investig tional Product	Table 3: Investigational Product
One application of sheets of no more than 10 StrataGraft skin tissues and applied to no more than 3 noncontiguous burn sites and applied to no more than approximately 1000 cm^2 total burn area to wounds with intact dermal elements./	On application of sheets of no more than ~~10~~ StrataGraft skin tissues and applied to no more than 3 noncontiguous burn sites and applied to no more than approximately ~~1000~~ cm^2 total burn area to wounds with intact dermal elements./	One application of sheets of no more than **20** StrataGraft skin tissues and applied to no more than 3 noncontiguous burn sites and applied to no more than approximately **2000** cm^2 total burn area to wounds with intact dermal elements./
Rationale:		
Review of safety data up to this point has shown no correlation between dosing and any safety signals. Based on that safety data, no identifiable risks were seen with doubling the allowable dose.		

Protocol Section/Issue/Rationale for Change	**Removed Text Displayed in Strikethrough Font**	**New Text Bolded**
Up to this point, the only expertise with larger wounds would be as seen in the real world, has been with compassionate use cases which do not have the structure of a clinical study. Doubling the allowable dose at this time, allows to demonstrate clinical study expertise and experience in larger treatment areas.		
Section 1 Synopsis Study Design In addition, a subset of 10 subjects with closed wounds (the first subjects who have wound closure and have consented) will be separately consented to have a biopsy performed for a histological evaluation of their healed skin architecture./ Study Design (continued)	Section 1 Synopsis Study Design In addition, a subset f 0 subjects with closed wounds ~~(the first subjects who have wound closure and have consented)~~ will be separately con ented to have a biopsy ~~performed for a histological evaluation of their healed skin architecture.~~ Study Design (continued)	Section 1 Synopsis Study Design In addition, a subset of 10 subjects **(sourced from across all the sites)** with closed wounds (the first subjects who have wound closure**, across all the sites**) will be separately consented to have a **punch** biopsy **(measuring 3 mm) taken from the center of the healed burn wound, and another punch biopsy measuring 3 mm taken from non-burned healthy skin. A histological evaluation of both samples will be done to analyze and contrast the skin architecture in the healed burn wound with healthy skin. The biopsy will happen at the study visit Week 12, regardless of when wound closure occurs.** Study Design (continued)

Protocol Section/Issue/Rationale for Change	**Removed Text Displayed in Strikethrough Font**	**New Text Bolded**
Wound assessments will include measurement of percent epithelialization, supported by assessments of photographs taken by the subject and/or taken by the clinical study site staff at study visits throughout the study./	Wound assessments will include measurement of percent epithelialization, ~~supported by assessments of~~ photographs taken by the subject and/or taken by the clinical study site staff at study visits throughout the study.	Wound assessments will include **measurements for average depth, length, and width for calculations of area and** percent epithelialization. **Wound assessments will be facilitated by** photographs taken by the subject and/or taken by the clinical study site staff at study visits throughout the study.
Section 4,2 Assessment of Potential Risks and Benefits	Section 4,2 Assessment of Potential Risks and Benefits	Section 4,2 Assessment of Potential Risks and Benefits
A subset of the first 10 subjects who achieve complete wound closure and have consented to study treatment will also undergo a biopsy of their healed StrataGraft-treated wound sites at Week 12 to histologically assess tissue architecture and any other histological tests as required.	A subset of ~~the first~~ 10 subject who achieve complete wound clo ure and have consented to study treatment will also undergo a biopsy of heir healed StrataGraft-treated wound sites at Week 12 to histologi ally assess tissue architecture and any othe hist logical tests as required.	
Section 6.1.1 Schedule of Assessments	Section 6.1.1 Schedule of Assessments	Section 6.1.1 Schedule of Assessments
Table 2: footnote j	Table 2: footnote j	Table 2: footnote j
A biopsy of a closed wound will be taken from a subgroup of 10 subjects.	~~A biopsy~~ of a closed wound will be taken from a subgroup of 10 subjects.	**Biopsies** of a closed wound **and of the normal skin** will be taken from a subgroup of 10 subjects.
Section 11 Other Assessments		**Section 11 Other Assessments**
{not formerly included}/		

Protocol Section/Issue/Rationale for Change	Removed Text Displayed in Strikethrough Font	New Text Bolded
Rationale: Provide clarity for the timing and the sample collection techniques for the biopsy collection. Clarification that the 10 subjects to be separately consented for biopsy are not limited to the first 10 subjects who have wound closure. Clarify biopsies and wound assessment measurements.		**A subset of 10 subjects with closed wounds (from subjects who have achieved wound closure, across all the clinical sites) will be separately consented to have a punch biopsy (measuring 3 mm) taken from the center of the healed burn wound, and another punch biopsy measuring 3 mm taken from non-burned healthy skin. A histological evaluation of both samples will be done to analyze and contrast the skin architecture in the healed burn wound with healthy skin. The biopsy will happen at the study visit Week 12, regardless of when wound closure occurs.** **Wound assessments will include measurements for average depth, length, and width for calculations of area and percent epithelialization. Wound assessments will be facilitated by photographs taken by the subject and/or taken by the clinical study site staff at study visits throughout the study.**
Section 1 Synopsis Inclusion Criteria Inclusion Criterion #3 3. Sufficient healthy skin identified and reserved as a donor site in the event that the	Section 1 Synopsis Inclusion Criterion #3 3. Sufficient healthy skin identified and ~~reserved~~ as a donor site in the event that the	Section 1 Synopsis Inclusion Criteria #3 3. Sufficient healthy skin identified and **designated** as a donor site in the event that

Protocol Section/Issue/Rationale for Change	**Removed Text Displayed in Strikethrough Font**	**New Text Bolded**
StrataGraft treatment site requires autografting/ Rationale: Updated to match the language in body of the protocol	StrataGraft treatment site requires autografting	the StrataGraft treatment site requires autografting
Section 1 Synopsis Study Design Enrollment will include subjects with a minimum of 3% and up to 49% TBSA thermal burn. Inclusion Criterion #4 3 to 49% TBSA of partial +/- full thickness thermal burns/ Section 7 Selection and Withdrawal of Subjects Inclusion Criterion #4 3 to 49% TBSA of partial +/- full thickness thermal burns/	Section 1 Synopsis Study Design Enrollment will include subjects w th a minimum of 3% and up to ~~49~~% TBSA thermal burn. Inclusion riterion #4 3 to ~~49%~~ TBSA of partial +/- full thickness thermal burns/ Section 7 Selection and Withdrawal of Subjects Inclusion Criterion #4 3 to ~~49%~~ TBSA of partial +/- full thickness thermal burns/	Section 1 Synopsis Study Design Enrollment will include subjects with a minimum of 3% and up to **50**% TBSA thermal burn **of partial** +/- **full thickness**. Inclusion Criterion #4 **3% up** to **<50%** TBSA of partial +/- full thickness thermal burns/ Section 7 Selection and Withdrawal of Subjects Inclusion Criterion #4 **3% up** to **<50%** TBSA of partial +/- full thickness thermal burns/

Protocol Section/Issue/Rationale for Change	Removed Text Displayed in Strikethrough Font	New Text Bolded
Rationale: Allows for including TBSA up to 49% but under 50%		
Section 1:Protocol Synopsis Exploratory Endpoint • Prescription drugs given for wound-related pain control/ • Antibiotics given for outpatient use at discharge Section 5.3 Exploratory Objectives Exploratory Endpoint • Prescription drugs given for wound-related pain control/ • Antibiotics given for outpatient use at discharge Section 6.1 Overall Study Design • Prescription drugs given for wound-related pain control/	Section 1:Protocol Synopsis Exploratory Endpoint • Prescription drugs given for wound-related pain control/ • ~~Antibiotics given for outpatient use at discharge~~ Section 5.3 Exploratory Objectives Exploratory Endpoint • Prescription drugs given for wound-related pain control/ • ~~Antibiotics given for outpatient use at discharge~~ Section 6.1 Overall Study Design	Section 1:Protocol Synopsis Exploratory Endpoint • Prescription drugs given **at discharge from the hospital** for wound-related **events including** pain control**, itch, psychotropics, and antibiotics** Section 5.3 Exploratory Objectives Exploratory Endpoint • Prescription drugs given **at discharge from the hospital** for wound-related **events including** pain control**, itch, psychotropics, and antibiotics** Section 6.1 Overall Study Design • Prescription drugs given **at discharge from the hospital** for wound-related **events including** pain control**, itch, psychotropics, and antibiotics**

Protocol Section/Issue/Rationale for Change	Removed Text Displayed in Strikethrough Font	New Text Bolded
• Antibiotics given for outpatient use at discharge/	• Prescription drugs given for wound-related pain control/ • ~~Antibiotics given for outpatient use at discharge~~	
Section 6.1.1 Schedule of Assessments Prescription drugs given for wound-related pain control/ <previously not included>		Section 6.1.1 Schedule of Assessments • Prescription drugs given **at discharge from the hospital** for wound-related **events including** pain control**, itch, psychotropics, and antibiotics**
Section 10.2 Exploratory Objectives • Prescription drugs given for wound-related pain control/ • Antibiotics given for outpatient use at discharge/	Section 10.2 Expl ratory Objectives • Pr scription drugs given for wound-related pain control/ • ~~Antibiotics given for outpatient use at discharge~~	Section 10.2 Exploratory Objectives • Prescription drugs given **at discharge from the hospital** for wound-related **events including** pain control**, itch, psychotropics, and antibiotics**
Section 12.2.3 Exploratory Efficacy Endpoints • Prescription drugs given for wound-related pain control/ • Antibiotics given for outpatient use at discharge/	Section 12.2.3 Exploratory Efficacy Endpoints • Prescription drugs given for wound-related pain control/ • ~~Antibiotics given for outpatient use at discharge~~	Section 12.2.3 Exploratory Efficacy Endpoints • Prescription drugs given **at discharge from the hospital** for wound-related **events including** pain control**, itch, psychotropics, and antibiotics**

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Rationale: The intent is to capture prescriptions are meant to refer to medications with which subjects are sent home and not what they receive in the hospital. We intend to collect all medications for wound-related concerns: pain, itch, new psychotropics, and antibiotics.		

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Section 1 Protocol Synopsis Exclusion Criteria: Study-specific criteria: 8. Participation in a study of an investigational device, pharmaceutical, or biologic drug within 90 days prior to enrollment/ Section 7.2 Subject Exclusion Criteria 9. Participation in a study of an investigational device, pharmaceutical, or biologic drug within 90 days prior to enrollment/ Rationale: Nutritional and observational studies should not impact eligibility in this study.		Section 1 Protocol Synopsis Exclusion Criteria: Study-specific criteria: 11. Participation in a study of an investigational device, pharmaceutical, or biologic drug within 90 days prior to enrollment **(Participants in nutritional or non-interventional observational studies where no investigational product or device is given or administered will not be excluded.)** Section 7.2 Subject Exclusion Criteria 12. Participation in a study of an investigational device, pharmaceutical, or biologic drug within 90 days prior to enrollment **(Note: Participants in nutritional or non-interventional observational studies where no investigational product or device is given or administered will not be excluded.)**

Protocol Section/Issue/Rationale for Change	**Removed Text Displayed in Strikethrough Font**	**New Text Bolded**
Section 4.3 Summary of Relevant Clinical Studies Seventy-one subjects were enrolled and the last subject is expected to complete all study procedures in March 2020. To date, no StrataGraft-related SAEs have been reported. Rationale: The Phase 3 study details were updated.	Section 4.3 Summary of Relevant Clinical Studies ~~Seventy-one subjects were~~ enrolled and the last subject ~~is expected to complete~~ all study procedures in March 2020. ~~To date, no~~ StrataGraft-related SAEs ~~have been~~ reported.	Section 4.3 Summary of Relevant Clinical Studies **The number of** enrolled **subjects was 71** and the last subject **completed** all study procedures in March 2020. **No** StrataGraft-related SAEs **were** reported.
Section 6.1 Overall Study Design • The time to complete wound closure without autograft placement (verified with confirmation assessment); the investigator will assess the wound in person or alternatively assess a photo provided by the subject if the subject misses a visit (the subject will have a photo taken and send them to a photo repository, beginning at discharge then weekly until Week 12 and then bi-weekly until Week 24)./ Rationale: Clarification of collection of data for time to complete wound closure endpoint.	Section 6.1 Overall St dy Design The time to compl te wound closure without a togr ft placement (verified with confirmation asse sment); the investigator will asses the wound in person or alterna ively assess a photo provided by the subject if the subject misses a visit (the subject will have a photo taken and send them to a photo repository, beginning at discharge then weekly until Week 12 and then ~~bi-weekly~~ until Week 24).	Section 6.1 Overall Study Design • The time to complete wound closure without autograft placement (verified with confirmation assessment). **For in-person visits,** the investigator will assess the wound in person or alternatively assess a photo provided by the subject if the subject misses a visit. **For the weeks in between onsite visits,** the subject will have a photo taken and send them to a photo repository beginning at discharge then weekly until Week 12 **and then every other week** until Week 24. **These photos will also be assessed by the principle investigator.**
Section 6.1.1 Schedule of Assessments		Section 6.1.1 Schedule of Assessments

Protocol Section/Issue/Rationale for Change	Removed Text Displayed in Strikethrough Font	New Text Bolded
{not formerly included} Consent for registry added as separate entry/ Rationale: For clarification for *when* collection of consent for the registry is possible: presented as separate entry from initial informed consent and clarified time points for collection {Immunology testing added}/ Rationale: Serves to supplement the PRA data in the StrataGraft clinical development program, by providing additional HLA I and II findings associated with the use of StrataGraft skin tissue.		**Consent for direct contact by Sponsor and safety registry post study** Section 16.3 Written Informed Consent **Consent must also be obtained for direct contact by Sponsor for the post study safety registry during the study period.** **Section 12.2.3 Immunology** **Blood collection for PRA testing (HLA I and II) at Day 1 (Baseline), Week 4, and Week 12.** **Section 12.3.5.3 Immunology Assessments** **Immunological evaluations will include PRA with HLA class I and II screening and testing for allelic reactivity.**

Protocol Section/Issue/Rationale for Change	**Removed Text Displayed in Strikethrough Font**	**New Text Bolded**
{Visit windows expanded by adding footnotes to the Schedule of Assessments table}/ Rationale: Increases assessment windows in case of publicly stated emergencies.		**a In public state of emergency situations, the Weeks 1 and 2 visit windows can be expanded to include ± 5 days.** **b In public state of emergency situations, the Week 4 visit window can be expanded to include ± 12 days.** **c In public state of emergency situations, the Weeks 8, 12, and 24 visit windows can be expanded to include ± 14 days.**
Section 6.5 Provision for Remote Assessments {not formerly included}/ Rationale: In case of public stated emergencies, include provision for remote assessments and expanded windows for assessments collected during physical visits to the clinics.		**Section 6.5 Provision for Remote Assessments** **For publicly stated emergency situations where there are extenuating circumstances that prohibit physical visits to the clinical site or when the safety of subjects may be compromised by physical visits to the site, provisions for remote assessments have been addressed.** **For publicly stated emergency situations, the visit windows can be expanded as follows.** **Weeks 1 and 2 ± 5 days** **Week 4 ± 12 days** **Weeks 8, 12, 24 ± 14 days**

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		Refer to the Manual of Procedures for a list of those assessments; remote collection of certain clinical assessments may be allowed.

Section 6.6 Criteria for Study Stopping Subject enrollment will be stopped pending discussions with the Data and Safety Monitoring Board (DSMB) and/or FDA if any of the following SAEs occur: • Necrotizing soft tissue infection of the study wound attributed to StrataGraft skin tissue • Severe acute hypersensitivity reaction attributed to StrataGraft skin tissue • Death attributed to StrataGraft skin tissue Safety will be monitored by an independent DSMB. In the event that one of the listed SAEs occurs, the FDA, local institutional review board (IRB), and DSMB will be notified according to the decision tree for Reporting SAE as presented in the Manual of Procedures. The medical monitor will review the safety data associated with the adverse reaction with the clinical investigator and generate a summary narrative. The medical monitor and DSMB will conduct a comprehensive review of the safety data that will be submitted to the FDA prior to resumption of subject enrollment./	Section 6.6 Criteria for Study Stopping Subject enrollment will be stopped ~~pending discussions with the Data and Safety Monitoring Board (DSMB) and/or FDA~~ if any of the following SAEs occur: • Necrotizing soft tissue infection of the study wound attributed to StrataGraft skin tissue • Severe acute hypersensitivity reaction attributed to StrataGraft skin tissue • Death attributed o StrataGraft skin tiss e ~~Safety will be monitored by an independent DSMB.~~ In the e ent that one of the listed SAEs occurs the FDA, local institutional rev w board (IRB), and DSMB will be notified according to the decision tree for Reporting SAE as presented in the Manual of Procedures.-The medical monitor will review the safety data associated with the adverse reaction with the clinical investigator and generate a summary narrative. The medical monitor ~~and DSMB will~~ conduct a comprehensive review of the safety data that will be submitted to the FDA prior to resumption of subject enrollment.	Section 6.6 Criteria for Study Stopping Subject enrollment will be stopped if any of the following SAEs occur: • Necrotizing soft tissue infection of the study wound attributed to StrataGraft skin tissue • Severe acute hypersensitivity reaction attributed to StrataGraft skin tissue • Death attributed to StrataGraft skin tissue In the event that one of the listed SAEs occurs, the FDA, and the local institutional review board (IRB~~)~~ will be notified according to the decision tree for Reporting SAE as presented in the Manual of Procedures. The Medical Monitor will review the safety data associated with the adverse reaction with the clinical investigator and generate a summary narrative. The Medical Monitor, **the Global Safety Lead and the Clinical Trial Lead** will conduct a comprehensive review of the safety data that will be submitted to the FDA prior to resumption of subject enrollment. **An independent adhoc Safety Committee made up of DSMB members familiar**

Protocol Section/Issue/Rationale for Change	Removed Text Displayed in Strikethrough Font	New Text Bolded
Rationale: The FDA review team agreed that, since this an open-label, single-arm study design, and, given the lack of safety concerns throughout product development, the DSMB annual review is not necessary. As agreed, the use of a DSMB has been removed from this protocol. Safety data will be reviewed by the Medical Monitor, the Global Safety Lead and the Clinical Trial Lead.		**with other StrataGraft studies will be on stand-by to serve as external adjudicators in the event that any of the prior listed SAEs occurs and study enrollment is halted. The Safety Committee working with the Medical Monitor, the Global Safety Lead and the Clinical Trial Lead will determine if and when the study may be restarted.**
Section 8.1 Description of Study Treatment Dosage Form StrataGraft skin tissue is a cryopreserved, viable, bilayer, allogeneic human skin substitute. It is produced in a rectangular, approximately 100 cm^2 format, and supplied loosely adherent to a polycarbonate membrane of a Transwell® insert (Corning, NY). StrataGraft skin tissue is stored at -70°C to -90°C until thawed for use. The hold solution that must be used with the StrataGraft skin tissue must be stored at 2° to 8°C until removed on the day prior to surgery./	Section 8.1 Description of Study Treatment Dosage Form Stra Graft skin tissue ~~is a cryopreserved, viable, bilayer, allogeneic human skin substitute. It is produced in a rectangular, approximately 100 cm^2 format, and supplied loosely adherent to a polycarbonate membrane of a Transwell® insert (Corning, NY).~~ StrataGraft skin tissue is stored at -70°C to -90°C until thawed for use. The hold solution that must be used with the StrataGraft skin tissue must be stored at 2° to 8°C until ~~removed on the day prior to~~ surgery.	Section 8.1 Description of Study Treatment Dosage Form **StrataGraft skin tissue is an off-white rectangular sheet of approximately 100 cm^2 (approximately 8 cm by 12.5 cm), consisting of a viable, bioengineered, regenerative skin construct derived from human keratinocytes grown on gelled collagen containing human dermal fibroblasts.** StrataGraft skin tissue is stored at -70°C to -90°C until thawed for use. The hold solution that must be used with the

Protocol Section/Issue/Rationale for Change	**Removed Text Displayed in Strikethrough Font**	**New Text Bolded**
Rationale: Revised according to text in the current product label.		StrataGraft skin tissue must be stored at 2° to 8°C until **required for** surgery.
Section 8.2 Concomitant Medications All concomitant medications, including the use of antibiotics, must be recorded in the eCRF after the consent form is signed and throughout the study period. Systemic and topical antibiotics/antimicrobials may be used at the discretion of the clinical investigator with the exception of sulfa- and silver-containing antimicrobials and silver-containing dressings. Prior to StrataGraft skin tissue placement, chlorhexidine and iodine can be applied to burn sites for wound preparation but must be thoroughly rinsed off prior to StrataGraft placement. After StrataGraft skin tissue placement, further use of these antiseptics is prohibited. Additionally, investigational agents may not be used for the duration of study period. All other specific concomitant medications will have no restrictions. Intravenous fluids generally used to maintain hydration are not considered a concomitant medication./ Rationale:	Section 8.2 Concomitant Medications All concomitant medications, including the use of antibiotics, must be recorded in the eCRF after the consent form is signed and throughout the study period. Systemic and topical antibiotics/antimicrobials may be used at the discretion of the clinical investigator with the exc ption of sulfa and silver-containing antimicrobials and silver-containing dr ssings. Prior to StrataGraft skin tissue plac ment, chlorhexidine ~~and iodine~~ can be applied to burn sites for wound pr paration but must be thoroughly rinsed ff prior to StrataGraft placement. After StrataGraft skin tissue placement, further use of these antiseptic~~s~~ is ~~prohibited~~. Additionally, investigational agents may not be used for the duration of study period. All other ~~specific~~ concomitant medications ~~will have no restrictions.~~ Intravenous fluids generally used to maintain hydration are not considered a concomitant medication.	Section 8.2 Concomitant Medications All concomitant medications, including the use of antibiotics, must be recorded in the eCRF after the consent form is signed and throughout the study period. Systemic and topical antibiotics/antimicrobials may be used at the discretion of the clinical investigator with the exception of sulfa**mylon** and silver-containing antimicrobials and silver-containing dressings. **The use of sulfamylon and silver containing/releasing antimicrobials and dressings is not recommended as they are thought to interfere with the viability of the living cells in StrataGraft skin tissue.** Prior to StrataGraft skin tissue placement, and chlorhexidine can be applied to burn sites for wound preparation but must be thoroughly rinsed off prior to StrataGraft placement. After StrataGraft skin tissue placement, further use of this antiseptic on the StrataGraft treatment site is **also not recommended**. **Use of any of the aforementioned antiseptics at the discretion of the Principal Investigator, after StrataGraft skin tissue placement, would not be considered a protocol**

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The prescribing information should be consistent with the intended product labelling.		**deviation. Additionally, investigational agents may not be used for the duration of study period.** All other concomitant medications **are unrestricted.** Intravenous fluids generally used to maintain hydration **and general anesthetic given during surgery need not be captured as concomitant medications.**
Section 8.4 Randomization and Blinding This study is designed as an open-label, single arm study. No randomization will be conducted, and no blinding is required for the study. /		Section 8.4 Randomization and Blinding This study is designed as an open-label, single arm study **in which all subjects receive StrataGraft skin tissue and all other burn wounds will be treated per institutional SoC**. No randomization will be conducted, and no blinding is required for the study.
Section 9.5 Study Administration Once the designated study site(s) have been excised and the subject is determined to meet all eligibility criteria, StrataGraft skin tissue will be meshed from 0.25 to up to 1:1 and secured to the wound with sutures, staples, or tissue adhesives and then dressed with a non-adherent, porous dressing. Secondary dressings will be applied that are designed to maintain a moist wound environment and protect tissue from maceration and external contamination. All dressings, including the primary dressing,	Section 9.5 Study Administration Once the designated study site(s) have been excised and the subject is determined to meet all eligibility criteria, StrataGraft skin tissue will be meshed ~~from 0.25 to~~ up to 1:1 and secured to the wound with sutures, staples, or tissue adhesives and then dressed with a non-adherent, porous dressing. Secondary dressings will be applied that are designed to maintain a moist wound environment and protect tissue from maceration and external contamination. All dressings~~, including the primary dressing,~~	Section 9.5 Study Administration Once the designated study site(s) have been excised and the subject is determined to meet all eligibility criteria, StrataGraft skin tissue will be meshed up to 1:1 and secured to the wound with sutures, staples, or tissue adhesives and then dressed with a non-adherent, porous dressing. Secondary dressings will be applied that are designed to maintain a moist wound environment and protect tissue from maceration and external contamination.

will be changed per institutional SoC until healing, or as long as deemed clinically necessary by the Investigator. Silver-containing dressings are prohibited from use in this study. No adhesive dressing, tape or adhesive strips, may be applied directly on the StrataGraft skin tissue covered site or its periphery during the study period. Prior to StrataGraft skin tissue placement, chlorhexidine and iodine can be applied to burn sites for wound preparation, but must be thoroughly rinsed off before StrataGraft placement. After StrataGraft skin tissue placement, further use of these antiseptics is prohibited./ Rationale: The intent is to standardize the timing of changes and type of dressings to prevent accidental premature disruption of StrataGraft skin tissue.	will be changed per institutional SoC until healing, or as long as deemed clinically necessary by the Investigator. Silver-containing dressings are ~~prohibited from~~ use in this study. No adhesive dressing, tape or adhesive strips, may be applied directly on the StrataGraft skin tissue covered site or its periphery during the study period. Prior to StrataGraft skin tissue placement, chlorhexidine ~~and iodine~~ can be applied to burn sites for wound preparation, but must be thoroughly rinsed off before StrataGraft placement. After StrataGraft skin tissue placement, further use of ~~these~~ antiseptic~~s~~ is ~~prohibited~~.	Silver-containing dressings are **not recommended for** use in this study. No adhesive dressing, tape or adhesive strips, may be applied directly on the StrataGraft skin tissue covered site or its periphery during the study period. Prior to StrataGraft skin tissue placement, chlorhexidine can be applied to burn sites for wound preparation, but must be thoroughly rinsed off before StrataGraft placement. After StrataGraft skin tissue placement, further use of **this antiseptic is not recommended.** **It is not expected that StrataGraft skin tissue will incorporate into the wound bed due to vascular ingrowth as is seen with autologous skin grafts. It is anticipated that maximal benefit from treatment with StrataGraft skin tissue would come after maintenance of contact with the clean wound bed for as long as possible. Therefore, it is important to be careful during dressing changes during the first few weeks following placement.** **Week 1: The non-adherent porous contact layer dressing should remain anchored in place for at least 3 days in order to prevent dislodging of the StrataGraft skin tissue. The frequency of changes of the secondary dressings is at the discretion of the Investigator, paying attention to the precautions listed below.**

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		Weeks 2 to 3: The contact layer dressing may be removed with care not to dislodge any remaining adherent StrataGraft skin tissue. Replacement of a nonadherent contact layer is recommended. All secondary dressings and frequency of changes are at the discretion of the Investigator paying attention to the precautions listed below. The healing epidermis beneath StrataGraft skin tissue may result in small areas of drying and lifting of StrataGraft changing the appearance to one that may be described as shabby or flaky. Over time, the dried StrataGraft skin tissue will flake off during daily washing and wound care per institutional standards of care as the new, healthy epidermis expands beneath it. The healing wound still requires protection from shear forces as the new skin matures. **Week 4 through remainder of study:** All dressings will be changed per institutional SoC until healing, or as long as deemed clinically necessary by the Investigator. Silver-containing dressings are **not recommended for** use in this study. No adhesive dressing, tape or adhesive strips, may be applied directly on the StrataGraft skin tissue covered site or its periphery

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		during the study period. Prior to StrataGraft skin tissue placement, chlorhexidine can be applied to burn sites for wound preparation, but must be thoroughly rinsed off before StrataGraft placement. After StrataGraft skin tissue placement, further use of **this antiseptic is not recommended.**
Section 6.1.1 Schedule of Assessments Table 2: Footnote i A weekly photo taken by subject (or designate) of the treatment site(s) for the first 12 weeks and then biweekly to Week 24.	Section 6.1.1 Schedule of Assessments Table 2: Footnote i A weekly photo taken by subject (or designate) of the treatment site(s) for the first 12 weeks and then ~~biweekly to Week 24~~.	Section 6.1.1 Schedule of Assessments Table 2: Footnote i A weekly photo taken by subject (or designate) of the treatment site(s) for the first 12 weeks and then **every other week to Week 24. Photos submitted during a week when there's no in-person visit would serve as an allowable proxy for observing wound characteristics. If a subject's wound is noted to be closed for the first time via a submitted photo that should prompt a confirmation of wound healing visit 2 weeks later.**
Section 10 Assessment of Other Pre-Specified Endpoints Photo-documentation Photographs will be taken by the clinician to supplement clinical assessment of complete wound closure, confirmed wound closure, durable wound closure and the POSAS assessments (eg, appearance and	Section 10 Assessment of Other Pre-Specified Endpoints Photo-documentation Photographs will be taken by the clinician to supplement clinical assessment of complete wound closure, confirmed wound closure, durable wound closure and the POSAS assessments (eg, appearance and	Section 10 Assessment of Other Pre-Specified Endpoints Photo-documentation Photographs will be taken by the clinician to supplement clinical assessment of **percentage epithelialization,** complete wound closure, confirmed wound closure, durable wound closure and the POSAS assessments (eg, appearance and cosmesis)

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cosmesis) of the treatment sites. Photographs taken and submitted by the subject (or other person designated by the subject) may be used for evidence of wound characteristics if a visit is missed or for an unscheduled visit. Photo-documentation is submitted by the subject beginning at discharge then weekly until Week 12 and then bi-weekly until Week 24. See Manual of Procedures for specific instructions regarding the methodology for obtaining photographs./ Rationale: These photos are only possible at the discretion of the PI and we want clarify that assessment of wound closure is primarily intended to be based on the PI's visual and clinical judgement at dressing change. The need to capture photos serves as supporting evidence of closure and generally intended as secondary evidence to the PI's visual assessment. Language was added around the use of these photos to assess wound characteristics.	cosmesis) of the treatment sites. Photographs taken and submitted by the subject (or other person designated by the subject) may be used for evidence of wound characteristics if a visit is missed or for an unscheduled visit. Photo-documentation is submitted by the subject beginning at discharge then weekly until Week 12 and then ~~bi-weekly~~ until Week 24. See Manual of Procedures for specific instructions regarding the methodology for obtaining photographs.	of the treatment sites. Photographs taken and submitted by the subject (or other person designated by the subject) may be used for evidence of wound characteristics if a visit is missed or for an unscheduled visit. Photo-documentation is submitted by the subject beginning at discharge then weekly until Week 12 and then **every other week** until Week 24. **These subject submitted photos are only possible if the PI approves the subject to take off their dressings at home. In the event, the dressings are not allowed to be changed at home, no subject photos will be expected or required. Photos submitted during weeks when there's no in-person visit would serve as an allowable proxy for observing wound characteristics. If a subject's wound is noted to be closed for the first time via a submitted photo that should trigger a confirmation of wound healing visit 2 weeks later**. See Manual of Procedures for specific instructions regarding the methodology for obtaining photographs.
Section 12.2.4 Regrafting and Delayed Wound Healing {not formerly included}/		**Section 12.2.4 Regrafting and Delayed Wound Healing** **In the event that a StrataGraft treated area needs to be regrafted with either an autograft or a xenograft after treatment**

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Rationale: Graft failure is not an adverse event as it is a failure of efficacy (defined as reepithelialization) rather than being a safety concern.		**with StrataGraft skin tissue, the event would not be marked as an AE, but rather as a treatment failure. In the event that there is an accompanying wound degradation event occurring simultaneously such as infection that results in delayed wound healing, the delayed wound healing secondary to the ongoing infection can be listed as an AE or SAE as applicable. If that infective process eventually warrants a regrafting, the regrafting should still be marked as a treatment failure and not an AE.**
Section 12.2.3 Immunology {not formerly included}/ Rationale: Serves to supplement the PRA data in the StrataGraft Clinical Development program, by additionally providing HLA I and II findings associated with the use of StrataGraft skin tissue.		**Section 12.2.3 Immunology** **Blood collection for PRA testing (HLA I and II) will be conducted at Day 1 (Baseline), Week 4, and Week 12.**
Section 12.3.5.4 Pregnancy Testing A urine pregnancy test for women of child-bearing potential will be performed at Screening and all positive urine tests will be confirmed with a serum pregnancy test.	Section 12.3.5.4 Pregnancy Testing A ~~urine~~ pregnancy test for women of child-bearing potential will be performed at Screening ~~and all positive urine tests will be confirmed with a serum pregnancy test~~.	Section **12.3.5.4** Pregnancy Testing A **serum** pregnancy test for women of child-bearing potential will be performed at Screening **using the local laboratory**. Should a pregnancy be confirmed after

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Should a pregnancy be confirmed after placement of StrataGraft, the pregnancy will be reported as a special event (not an AE). Since StrataGraft skin tissue is a single application, the subject will continue with all scheduled study evaluations. Pregnant subjects will be followed until post-partum and the outcome of the pregnancy will be reported./ Rationale: This serves to eliminate the possibility of false negatives that are results occasionally returned with the urine HCG test.	Should a pregnancy be confirmed after placement of StrataGraft, the pregnancy will be reported as a special event (not an AE). Since StrataGraft skin tissue is a single application, the subject will continue with all scheduled study evaluations. Pregnant subjects will be followed until post-partum and the outcome of the pregnancy will be reported.	placement of StrataGraft, the pregnancy will be reported as a special event (not an AE). Since StrataGraft skin tissue is a single application, the subject will continue with all scheduled study evaluations. Pregnant subjects will be followed until post-partum and the outcome of the pregnancy will be reported.
Section 12.3.2 Other Pre-specified Endpoint Analyses The time to first complete wound closure (verified with confirmation assessment) will be analyzed by the Kaplan-Meier estimation method. The period for this analysis is calculated as (the date of having the first event – the date of Day 1 + 1). Subjects not having any event during the study will have their time censored at the last available date in the study. Kaplan-Meier estimates by StrataGraft treatment area with confirmed wound closure will be presented for the	Section ~~12~~.3 2 Other Pre-specified Endpoint Analyses The time to first complete wound closure (verified with confirmation assessment) will be analyzed by the Kaplan-Meier estimation method. The period for this analysis is calculated as (the date of having the first event – the date of Day 1 + 1). Subjects not having any event during the study will have their time censored at the last available date in the study. Kaplan-Meier estimates by StrataGraft treatment area with confirmed wound closure will be presented for the	Section **13**.3.2 Other Pre-specified Endpoint Analyses The time to first complete wound closure (verified with confirmation assessment) will be analyzed by the Kaplan-Meier estimation method. The period for this analysis is calculated as (the date of having the first event – the date of Day 1 + 1). Subjects not having any event during the study will have their time censored at the last available date in the study. Kaplan-Meier estimates by

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following categories: ≤ 250 cm^2, 250 ≤ 500 cm^2, > 500 cm^2./ Rationale: Three categories revised to 2 categories to be consistent with Section 5.4 and Section 10, as 3 categories may not result in separation between the categories.	following categories: ~~≤ 250 cm^2, 250 ~~≤ 500 cm^2, > 500 cm^2.	StrataGraft treatment area with confirmed wound closure will be presented for the following categories: ≤ 500 cm^2, > 500 cm^2.
Section 18, List of References References were updated		
Globally, minor formatting and editorial changes were made.		

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