Official Title: A Phase 3 Multicenter, Single-Arm, Open-Label Study Evaluating the Safety, Tolerability and Efficacy of StrataGraft® Construct in Pediatric Subjects with Deep Partial Thickness (DPT) Thermal Burns

NCT Number: NCT05517902

Document, Version and Date: Protocol, Version 3.0, 26 September 2023

STRATAGRAFT®

(ALLOGENEIC CULTURED KERATINOCYTES AND DERMAL FIBROBLASTS IN MURINE COLLAGEN-DSAT)

PROTOCOL NUMBER:	**MNK15011001**
PROTOCOL NAME:	A Phase 3 Multicenter, Single-Arm, Open-Label Study Evaluating the Safety, Tolerability and Efficacy of StrataGraft® Construct in Pediatric Subjects with Deep Partial Thickness (DPT) Thermal Burns
VERSION NUMBER/DATE:	Version 3, dated 26 Sep 2023
SHORT TITLE:	StrataSTEPS (StrataGraft Safety, Tolerability and Efficacy in Pediatric Subjects)
SPONSOR NAME	Stratatech Corporation, a Mallinckrodt Company
REGISTERED	510 Charmany Drive, Suite 150
ADDRESS:	Madison, WI 53719
US FDA IND Number:	010,113

SIGNATURE PAGE

Sponsor's Approval

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

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

Responsible Medical Officer:

Refer to e-signature page

[redacted] Date

ACKNOWLEDGEMENT OF RECEIPT AND UNDERSTANDING OF SPONSOR STUDY MATERIALS

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

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

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

PRODUCT:

StrataGraft®

STUDY:

StrataSTEPS - Protocol MNK15011001

PRINCIPAL/COORDINATING INVESTIGATOR(S)

Name:

Title:

Date:

Refer to e-signature page

Name Date

SUMMARY OF CHANGES FOR AMENDMENTS

Version 3 includes changes related to modifications in the xenotransplantation product requirements and prohibitions, which are reflected in Sections 4.4 and 11.9.1.5. Administrative issues and clarifications show changes in Section 1 (Synopsis) and Sections 6.1, 6.8, 8.2, 9.3, and 11. Appendix 6 is a table of the summary of changes.

1. SYNOPSIS

Name of Sponsor/Company: Stratatech Corporation, a Mallinckrodt Company		
Name of Investigational Product: StrataGraft® Construct		
Name of Active Ingredient: StrataGraft is a viable and metabolically active allogeneic human NIKS keratinocytes and human dermal fibroblasts cellularized layered scaffold.		
Protocol Number: MNK15011001	**Phase: 3**	**Country: US**
Title of Study: A Phase 3 Multicenter, Single Arm, Open-label Study Evaluating the Safety, Tolerability and Efficacy of StrataGraft® Construct in Pediatric Subjects with Deep Partial-Thickness (DPT) Thermal Burns		
Study center(s): Approximately 10 sites		
Objectives: **Primary:** To evaluate whether StrataGraft treatment promotes wound closure and reduces or eliminates the need for donor site harvest and autografting in a pediatric population with thermal burns that contain intact dermal elements and for which autografting would be part of standard of care (deep partial-thickness [DPT] burns). **Study Design:** This is a prospective, open-label, single -arm, age-stratified study to examine the safety and efficacy of StrataGraft construct in the treatment of pediatric subjects with thermal burns that contain intact dermal elements and for which autografting would be part of standard of care (deep partial-thickness [DPT] burns). This study is designed to assess the safety and efficacy of StrataGraft in the treatment of DPT thermal burns, defined as those that contain intact dermal elements and for which excision/debridement and autografting are clinically indicated.		
Methodology: Approximately 50 subjects will be enrolled into one of two age-based cohorts: 2 to < 12 years (up to n = 40) and 12 to ≤ 17 years (up to n = 10). The proposed study population will include pediatric subjects with thermal injuries covering no more than 30% of their total body surface area (TBSA) with at least 0.5% TBSA DPT thermal burn. Each subject must also have a sufficient area of healthy skin available for use as a donor site in the event that autografting is clinically necessary. Study assessments will include the incidence of adverse events (AEs), including wound infection, and additionally monitoring of vital signs, clinical laboratory values, immunological values (where possible), wound closure, including any autografting, and skin quality of the treatment site.		
Number of patients (planned): Approximately 50 subjects are planned to be enrolled.		

Main criteria for inclusion: An included subject will be or have:

1. Aged 2 through 17 years, inclusive, at the time of consent
2. Written informed consent from parent(s) or legal guardian(s) and assent from the child when appropriate, as determined by the Institutional Review Board (IRB), consistent with regulatory criteria and requirements.
3. Sufficient healthy skin available and reserved as a donor site in the event that the StrataGraft treatment site requires autografting.
4. Thermal burns of no more than a total of 30% TBSA.
5. Consenting adult(s) is/are able and willing to attend/bring child to the scheduled visits and comply with study procedures.
6. Study treatment sites that are DPT in depth (ie, containing dermal elements) and for which excision and autografting are clinically indicated as assessed by the investigator, and located on the torso or extremities.
7. Study treatment area(s) totaling 0.5% to 10% TBSA and may be composed of up to 3 non-contiguous areas located on the same extremity or plane of the torso.

Main criteria for exclusion: Subjects may not be or have:

1. Receiving systemic immunosuppressive therapy and/or systemic corticosteroids (inhaled corticosteroids are permitted).
2. Concurrent trauma, conditions, and/or personal situations that, in the opinion of the investigator, may compromise subject safety or the study objectives.
3. A burn injury that occurred ≥ 14 days prior to planned StrataGraft application.
4. A proposed study treatment site that has been previously excised or autografted; located adjacent to an undebrided/unexcised burn area; demonstrates signs and symptoms of wound infection, per judgement of the clinical investigator; lies across joints or is located on the feet (ie, distal to the malleolus), hands (distal to the wrist), face, neck, buttocks, perineum, or genitalia.

Investigational product, dosage and mode of administration: The investigational product is StrataGraft® Construct, a rectangular cellularized sheet approximately 100 cm^2, applied topically by the investigator following excision/debridement of the treatment site.

Duration of treatment: Following a screening period of up to 14 days following burn injury, qualified subjects will be enrolled and receive a single application of StrataGraft to 0.5% to 10% TBSA following debridement of non-viable tissue. Subjects will return to the clinic for visits weekly until confirmation of complete wound closure. Follow-up visits will be conducted at Week 12 and Months 6 and 12. Subjects will participate in the study for approximately 13 months, not including the screening period of up to 14 days.

Reference therapy, dosage and mode of administration: Not applicable.

Criteria for evaluation:

Primary efficacy endpoint: Percentage of subjects achieving confirmed complete closure of StrataGraft treatment sites on or before Week 12 without autograft placement. Confirmed complete wound closure is defined as complete skin re-epithelialization confirmed at 2 consecutive visits at least 2 weeks apart, but no later than Week 20.

Secondary ranked efficacy endpoints:

1. Mean of averaged percent area of StrataGraft treatment sites per subject closed at Week 12 without autograft placement
2. Number (%) of StrataGraft treatment sites with confirmed complete wound closure without autograft placement on or before Week 12
3. Mean of averaged percent area of StrataGraft treatment sites autografted per subject by Week 12

Exploratory endpoints and assessments:

- Mean percent area of StrataGraft treatment site closed without autograft placement at Week 8
- Mean Patient and Observer Scar Assessment Scale (POSAS) observer total score at Week 12, and Months 6 and 12.
- Changes in skin quality outcome (POSAS and Patient Scar Assessment Questionnaire [PSAQ] scores) across time.
- Incidence and severity of pain at the treatment site using EVENDOL (Evaluation Enfant Douleur, ie, Evaluation of Child Pain; observer or parent) or FPRS (Wong-Baker Faces Pain Rating Scale with 6 faces with expressions denoting degrees of pain; subject) over time.
- Percent of subjects with complete closure of StrataGraft treatment site without autografting at Weeks 6 and 8 and Months 6 and 12.
- Time to complete closure following application of StrataGraft.
- Mean percent wound closure over time from Day 21 through Month 12.
- Percent of subjects achieving and maintaining persistent wound closure at Months 6 and 12.
- Mean scar satisfaction based on PSAQ scores at Week 12 and Months 6 and 12.

Safety: The assessment of subject safety will consist of monitoring treatment-emergent adverse events, adverse events of special interest, serious adverse events, vital signs, and wound-related adverse events, including infection, throughout the study duration. These data will be episodically reviewed by a Data Monitoring Committee (DMC). Safety laboratory values (complete blood count with differential and comprehensive metabolic panel) will be measured along with panel reactive antibodies (PRA) and anti-bovine serum albumin (BSA) antibodies.

Statistical Overview: This pediatric study plans to enroll up to 50 subjects into one of two age cohorts: 2 to < 12 years (up to n = 40) and 12 to ≤ 17 years (up to n = 10). Analyses will be performed as the overall population. Analyses by age cohort will also be performed.

For the primary endpoint, number (%) and 95% confidence interval (CI) will be summarized based on the Intent-to-Treat population. Subjects with missing data will be imputed as nonresponders. The summary will also be performed based on all observed data, ie, excluding any missing data.

After the primary endpoint is successfully achieved, the ranked secondary efficacy endpoints will each be tested in a hierarchical manner in their ranked order, using a 2-sided confidence interval with 0.05 Type I error .

- The averaged percent area closed per subject will be calculated as, “Sum of percent area closed across treatment sites for a subject/the number of treatment sites on that subject”
- The percentage of StrataGraft treatment sites with confirmed complete wound closure without autograft placement on or before Week 12 will be calculated as [(Total number of StrataGraft treatment sites with confirmed complete wound closure without autografting on or before Week 12/Total number of treatment sites) x 100]

- The averaged percent area of StrataGraft treatment site per subject autografted by Week 12 will be calculated as (Sum of averaged percent area of StrataGraft treatment sites autografted for a subject/the number of StrataGraft treatment sites on a subject). It is a cumulative sum of percent area autografted for all nonmissing visits on or before Week 12.

For continuous efficacy endpoints, missing data will not be imputed. Missing or incomplete binary variables will be imputed as failures.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation	Explanation
AE	Adverse event
AESI	Adverse Event of Special Interest
BSA	Bovine serum albumin
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence Interval
CMP	Comprehensive metabolic panel
Complete closure	Complete re-epithelialization without drainage
Confirmed complete closure	Complete wound closure confirmed at 2 consecutive visits at least 2 weeks apart but no later than Week 20
DPT	Deep partial thickness, defined as a wound extending into the dermis but that contains intact dermal elements and for which excision/debridement and autografting are clinically indicated
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EVENDOL	EValuation ENfant DOuLeur, ie, Evaluation of Child Pain, a validated scale used to measure pain in pre-verbal children by assessing behavioral cues
FPRS	Wong–Baker Faces Pain Rating Scale, a validated scale of 6 faces with expressions denoting degrees of pain
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICC	Intraclass correlation coefficient
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional review board
ITT	Intent-to-treat
LB	Lower Bound
Persistence of Closure	Maintenance of wound closure for at least 3 months after confirmation of complete wound closure.
POSAS	Patient and observer scar assessment scale
PRA	Panel reactive antibodies

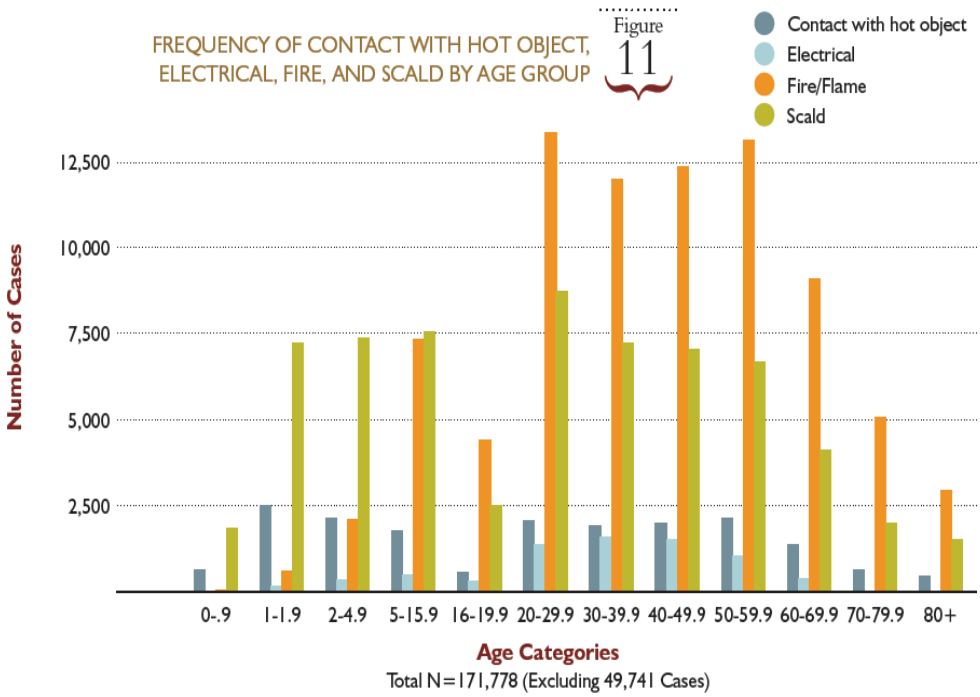
PSAQ	Patient Scar Assessment Questionnaire
SAE	Serious adverse event
SAP	Statistical Analysis Plan
StrataSTEPS	StrataGraft Safety, Tolerability and Efficacy in Pediatric Subjects
TBSA	Total body surface area
TEAE	Treatment emergent adverse event

4. INTRODUCTION

4.1. Background

Burn-related injuries are a leading cause of morbidity and mortality in children. Nearly a quarter of all burn injuries occur in children under the age of 16 years, most in children under the age of 5 years (Krishnamoorthy, 2012; Kramer, 2010). Every day in the United States, more than 300 children (age from 0 to 19 years) are treated for burn injuries in emergency departments, and 2 children die as a consequence of their burn injury (Borse, 2008). Approximately 90% of pediatric burns are caused by household accidents, with scald burns being most common amongst younger children and flame burns most common in the older child (National Burn Repository, 2019). Further, far more children under the age of 12 years are burned than are adolescents.

Figure 1: Number and Etiology of Burns by Age



Source: Figure 11, National Burn Repository, 2019.

Although wound healing and wound management do not differ between adults and children, there are differences between children and adults that may significantly affect how pediatric burn patients are managed. Young children have nearly 3 times the surface area to body mass ratio of adults, so they experience greater evaporative water losses and, hence, require greater fluid replacement. This difference in the surface area to body mass ratio also predisposes the child to hypothermia and increases their thermogenic metabolic demand. Finally, because of disproportionately thin skin in children, a burn that may initially appear to be partial thickness may instead declare itself to be full thickness within a day or 2 of injury, making burn depth assessment difficult.

After stabilization of the critical care issues in the burn-injured child, attention is directed toward burn wound management. The ultimate aim of wound management in burns 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 or surgical excision, 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 (Pietsch, 1985; Muller, 1994; Herndon, 1989), as well as hospital costs (Munster, 1994). Deep partial thickness (DPT) burns that are expected to take longer than 3 weeks to heal and full-thickness burns (with the exception of very small injuries) should be grafted, as this reduces hypertrophic scarring and results in better cosmesis (Heimbach, 1987; Chipp, 2017).

Excised areas are usually closed with autograft or with allograft, xenograft, or other skin substitute until autograft is available or the wound spontaneously closes. Availability of autologous donor tissue, however, is limited by the extent of the burn injury. In larger injuries, donor sites are often harvested repeatedly, increasing the likelihood of scarring at those sites. Further, the simple harvest of a donor site incurs acute pain as well as the potential for infection and scarring. As such, methods to reduce the amount of donor tissue needed to achieve wound closure are always sought.

StrataGraft is a viable, bioengineered, allogeneic, cellularized scaffold product composed of a differentiated epidermal compartment comprised of epidermal cells from a single human donor grown on a dermal equivalent composed of purified Type I animal collagen containing normal human fibroblasts from a second donor. The viable cells of StrataGraft produce and secrete a variety of growth factors, cytokines, and antimicrobial peptides. These factors are known to be involved in wound repair and tissue regeneration.

4.2. Study Rationale

StrataGraft is under development by Stratatech Corporation, a Mallinckrodt Company, as an alternative to autografting to promote the healing of acute thermal burns. A Biologics License Application for StrataGraft for the treatment of adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indicated (DPT burns) has received Food and Drug Administration (FDA) approval. Data from a Phase 3 study in adults demonstrated that 83% of wounds treated with a single application of StrataGraft achieved durable closure at Month 3 without autografting (Holmes, 2020). For that study, durable wound closure was defined as closure at 2 consecutive visits at least 2 weeks, but not more than 5 months apart and including or encompassing the Month 3 time point. Subjects with missing data were considered to have failed the endpoint.

Treating DPT burns with StrataGraft rather than autografting may be particularly beneficial for pediatric burn patients. This study is being conducted in order to evaluate the safety and efficacy of StrataGraft treatment in pediatric subjects with DPT burn injuries.

4.3. Assessment of Potential Risks and Benefits

Results to date in adults indicate that treatment with StrataGraft is well tolerated and no acute immune response has been reported. The most commonly reported adverse events (AEs) associated with StrataGraft are pruritus, blister, and hypertrophic scar.

Subjects in this study will undergo surgical excision/debridement of nonviable tissue in the burn wound. The risks associated with this procedure include pain and bleeding at the surgical site as well as potential complications of anesthesia, such as nausea/vomiting, chills, and sore throat.

All procedures and activities in this study, other than the actual application of StrataGraft, are generally accepted as standard of care for patients with thermal burns and are not considered to present any potential increased risk to the subjects. More detailed information about the known and expected benefit, risks, and reasonably expected AEs can be found in the StrataGraft Investigator's Brochure.

4.4. Xenotransplantation Considerations

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

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

A small amount of blood (3 mL), called an archival sample, will be collected before StrataGraft application. This sample could be used as a baseline to assess health issues that may be related to treatment. These samples will be used only for the purpose of responding to a request from FDA. Both archival samples and any associated subject information will be stored and used only as required and allowed by law.

5. OBJECTIVES AND ENDPOINTS

5.1. Primary Objective and Endpoint

5.1.1. Primary Efficacy Objective

To evaluate whether StrataGraft treatment eliminates or reduces the need for autografting and promotes wound closure in a pediatric population with thermal burns that contain intact dermal elements and for which autografting is clinically indicated (DPT burns).

5.1.2. Primary Efficacy Endpoint

Percentage of subjects achieving confirmed complete closure of StrataGraft treatment sites on or before Week 12 without autograft placement. Confirmed complete wound closure is defined as complete skin re-epithelialization confirmed at 2 consecutive visits at least 2 weeks apart but no later than Week 20.

5.1.3. Primary Outcome Measures:

- Percentage of participants achieving confirmed complete closure of StrataGraft treatment sites without autograft within 12 weeks of StrataGraft application, ie, percentage of participants whose burn healed after StrataGraft treatment without needing the doctor to treat the burn with skin cut from other parts of the patient's own body.
- Number of participants with treatment-emergent adverse events (TEAEs) that occurred between StrataGraft application and the end of the study (within 12 months of last data collection) and considered related to StrataGraft. This measure is not to be considered as a measure of study success.

5.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints, in hierarchical order, are:

1. Mean of averaged percent area of StrataGraft treatment sites per subject closed at Week 12 without autograft placement.
2. Number (%) of confirmed complete wound closures of the StrataGraft treatment sites on or before Week 12 without autograft placement.
3. Mean of averaged percent area of StrataGraft treatment sites per subject autografted by Week 12.

5.3. Exploratory Endpoints and Assessments

- Mean percent area of StrataGraft treatment site closed without autograft placement at Week 8.
- Mean Patient and Observer Scar Assessment Scale (POSAS) Observer total score at Week 12, and Months 6 and 12.

- Changes in skin quality outcome at StrataGraft treatment site (POSAS and Patient Scar Assessment Questionnaire [PSAQ] scores) across time.
- Incidence and severity of pain at the StrataGraft treatment site using EVENDOL (EValuation ENfant DOuLeur, ie, Evaluation of Child Pain; observer or parent) or FPRS (6 faces with expressions denoting degrees of pain; subject) rating scales over time.
- Percent of subjects with complete closure of StrataGraft treatment site without autografting at Weeks 6 and 12, and Months 6 and 12.
- Time to complete closure following application of StrataGraft.
- Mean percent wound closure of treated wound area over time from Day 21 through Month 12.
- Percent of subjects achieving and maintaining persistent wound closure at Months 6 and 12.
- Mean scar satisfaction based on PSAQ scores at Week 12, and Months 6 and 12.

5.4. Safety Endpoints and Assessments

The assessment of safety of StrataGraft in pediatric subjects.

Acceptable safety profile at Week 12 and Month 12, as determined by the Data Safety & Monitoring Committee (DMC; Section 13.6), with regard to:

- TEAEs.
- Serious adverse events (SAEs).
- Vital signs.
- Wound-related adverse events, including infection, throughout the study duration.
- Safety laboratory values (complete blood count with differential and comprehensive metabolic panel).
- Where practical, panel reactive antibodies (PRA) and anti-bovine serum albumin (BSA) antibodies.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a prospective, open-label, single arm study to examine the safety, tolerability and clinical efficacy of StrataGraft in the treatment of DPT thermal burns in pediatric subjects. The study population will include pediatric subjects ages 2 to 17 years, inclusive, with thermal burns that contain intact dermal elements and for which autografting would be part of standard of care. As previously discussed, far more pre-school and school-aged children are burned than adolescents. Qualified subjects will be enrolled into one of two age-based cohorts: 2 to < 12 years (up to n=40) and 12 to ≤ 17 years (up to n=10).

Informed consent will be obtained from parents/guardians and assent from the child, when appropriate, as determined by the IRB and consistent with regulatory criteria and requirements before any protocol-related assessments or procedures are conducted. After consent is provided, data collected during the course of admission and routine assessment may be abstracted from the medical record and used for study purposes.

Following a screening period of up to 14 days, subjects will be enrolled and receive a single application of StrataGraft to 0.5% to 10% total body surface area (TBSA), which may be composed of up to 3 non-contiguous areas located on the same extremity or plane of the torso.

Subjects will return to for weekly visits until complete wound closure of all study treatment sites is confirmed. Follow-up visits will be conducted at Week 12 and Months 6 and 12. Subjects will participate in the study for approximately 13 months, not including the screening period of up to 14 days. The Schedule of Study Events is provided in Table 2.

The duration of the study from first subject first visit to last subject last visit will depend upon the ability of the sites to identify and enroll eligible subjects. The study is expected to enroll subjects over a period of 12 to 18 months. The entire study is expected to require approximately 2.5 years to complete.

Safety assessments will include monitoring incidence of AEs, wound-related events, vital signs, clinical laboratory values (where possible), immunological markers (where possible), wound closure, pain, and scarring.

Subjects will undergo baseline assessments including a targeted physical examination and collection of clinical laboratory assessments during Screening. After enrollment and StrataGraft application, wound assessments, photographs, and solicitation of AEs will be performed at each study visit via telephone or video interaction if the subject is unable to attend the visit. However, wound closure may only be assessed at face-to-face visits. If not collected during Screening, clinical laboratory samples will be collected via venipuncture performed prior to StrataGraft application on Day 1. Immunological samples (monitoring of PRA and anti-BSA antibodies) will be collected prior to StrataGraft application, and again between Week 6 and Month 6 for all treated subjects.

A subject's study participation ends after the Month 12 visit. However, during the study period, should a subject return to the investigator for a follow-up visit not scheduled for the purposes of the study, the investigator, when feasible, will record any update on the subject's wound status

and safety information and report such information to the Sponsor using the data collection forms provided for such an Unscheduled visit.

6.2. Study Design Rationale

Deep partial thickness and full thickness burns that are expected to take longer than 3 weeks to heal are usually autografted, as this reduces the incidence of hypertrophic scarring and results in better cosmesis (Heimbach, 1987; Chipp, 2017). Donor sites are painful and patients have remarked that they are more painful than the burn injury itself (Romanelli, 2019; Sinha, 2017). Availability of autologous donor tissue is limited by the extent of the burn injury, and in larger injuries, donor sites may be repeatedly harvested, increasing the likelihood of scarring at those sites.

Clinical data from the STRATA2016 pivotal study of StrataGraft use for promoting the closure of DPT thermal burns in adult subjects demonstrated that more than 95% of subjects achieved closure without autografting after treatment with StrataGraft, thereby obviating the harvest of autograft and the pain associated with donor sites.

6.3. Treatment Rationale

StrataGraft is a viable, bioengineered, allogeneic, cellularized scaffold product that is anticipated to provide immediate wound coverage, aid in wound bed conditioning, and promote autologous tissue regeneration and wound closure while reducing or eliminating the need to harvest autologous donor tissue in adults.

Recent clinical data in adults demonstrate that treatment of DPT thermal burns with StrataGraft results in wound closure while reducing or eliminating the need for autograft. Although similar to the pivotal study in adults (ie, STRATA2016), this study of pediatric subjects will recruit not only younger subjects (ie, not adults) but also subjects with smaller TBSA burn. The reduced TBSA burn in pediatric subjects reflects the greater surface area to mass ratio of children compared to adults and the accompanying fluid status lability, limited physiologic reserves, as well as the reduced body size and attendant challenges.

The present study is being conducted to explore the efficacy and safety of StrataGraft in pediatric subjects with thermal burns containing dermal elements to better understand the product profile in a pediatric population.

6.4. Study Stopping Rules

In this study, the medical monitor as well as the DMC will assess safety and efficacy. The DMC will be independent of study conduct and their activities governed by a Charter.

Subject enrollment may be paused pending discussion with the DMC if any of the following events occur:

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

In the event that one or more of the above occurs, the Sponsor will be notified, per timelines in Section 11.12. 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 DMC will conduct a comprehensive review of the safety data, prior to resumption of subject enrollment.

6.5. End of Study Definition

A subject is considered to have completed the study if the subject has completed the Month 12 follow-up visit. The end of the study is defined as the completion of the final assessment for the last subject enrolled in the study.

6.6. Discontinuation of Study Treatment

Due to the nature of the study product and dressing requirements through the Day 7 visit, discontinuation of study investigational tissue product may not be feasible unless the subject manifests an adverse reaction within 7 to 10 days of application.

6.7. Subject Discontinuation/Withdrawal from the Study

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

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. Subjects withdrawn or discontinued from the study may be replaced and a new subject number assigned.

6.8. Schedule of Study Events and Assessments

Table 2: Schedule of Study Events and Assessments

	Screening Days -14 to -1	Day 1 (Baseline)	Day 7 ± 2 days	Day 14 ± 2 days	Day 21 ± 2 days	Day 28 ± 3 days	Weeks 5, 6, 7, etc [a] ± 3 days	Week 12 ± 1 week / Months 6 & 12 (± 4 weeks)
Informed consent/assent [b]	√							
Medical history and limited physical examination [o]	√							
Pregnancy test [c]	√							
Vital signs	√	√	√	√	√	√	√	√
Height and weight	√							√
Safety laboratory tests (CMP and CBC) [d]	√					√		
StrataGraft application		√						
Treatment site assessment [n]		√	√	√	√	√	√	√
Wound closure assessment [j]			√[j]	√[j]	√[j]	√[j]	√[j]	√[j]
Pain assessment (EVENDOL or FPRS) [k]			√	√	√	√	√	√
Assessment of need for continued hospitalization [l]			√	√	√	√	√	√
Photograph treatment sites		√[e]	√[f]	√[f]	√[f]	√[f]	√[f]	√[f]
Skin quality assessment (POSAS)				√[g]	√[g]	√[g]	√[g]	√[g]

	Screening Days -14 to -1	Day 1 (Baseline)	Day 7 ± 2 days	Day 14 ± 2 days	Day 21 ± 2 days	Day 28 ± 3 days	Weeks 5, 6, 7, etc [a] ± 3 days	Week 12 ± 1 week / Months 6 & 12 (± 4 weeks)
Satisfaction with scar (PSAQ)				√[g]	√[g]	√[g]	√[g]	√[g]
Concomitant medications and procedures [m]	√	√	√	√	√	√	√	√
Immunological samples [h] (PRA & anti-BSA)		√[h]					√[h]	√[h]
Archival samples [i]		√						
Adverse event monitoring	√	√	√	√	√	√	√	√

[a] Assessed weekly until wound confirmed as completely closed at a second visit at least 2 weeks after initial observation of closure but no later the Week 20, then assessed at Week 12 and Months 6 and 12.

[b] For purposes of this study, parents/legal guardians will consent on behalf of the child but assent from the child will also be solicited, when appropriate, as determined by the Institutional Review Board (IRB), consistent with regulatory criteria and requirements. Subjects who reach 18 years of age during their participation in the study will be re-consented.

[c] Females of childbearing potential only.

[d] Safety laboratory results will be collected prior to StrataGraft application and abstracted from the medical record, if available. If such results are not available, blood samples for study purposes will be collected as part of a clinically necessary venipuncture. A second safety laboratory assessment will be performed between Study Day 28 and Study Week 11, with results abstracted from the medical record, if available, or collected as part of a clinically necessary venipuncture.

[e] During the excision/debridement procedure, photographs will be taken of the study site(s) 1) pre-excision/debridement, 2) post-excision/debridement, and 3) post-StrataGraft application.

[f] Photograph all study treatment site(s) until complete closure, Week 12, or until the study burn is autografted; then photograph at Months 6 and 12. Photographs may be taken by trained caregivers or by study site personnel.

[g] Conducted at the first observation of closure, Week 12 (if closed prior), and Months 6 and 12.

[h] Immunological samples (monitoring of PRA and anti-BSA antibodies) will be collected prior to StrataGraft application, and one time again between Week 6 and Month 6 for all treated subjects

[i] Archival blood samples will be collected before application of StrataGraft and shipped for long-term storage.

[j] Wounds will be assessed for percent re-epithelialization at least weekly, beginning at the Day 7 visit, until complete wound closure is confirmed. Confirmation of closure will occur at least 2 weeks after initial observation of wound closure but no later than Week 20. Maintenance of closure will be assessed at each subsequent study visit following confirmation of wound closure.

[k] Assess pain only if wound is open.

[l] Note reason(s) for continued hospitalization such as pain management, fluid or nutritional status, infection risk, ongoing infection, inability to perform activities of daily living, insufficient social support, or other issues.
[m] Start/stop date, dose, unit, frequency, route and indication for all prior (taken within the 14 days prior to Day 1) and concomitant medications (taken from Screening through the Month 12 end of study visit) and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) administered will be recorded.
[n] Treatment site evaluations include assessment for signs & symptoms of infection or other adverse events and application of autograft.
[o] Medical history to include significant past morbidities, surgical procedures, etc. Limited physical exam will include review of systems and assessment of burn area, depth and location(s).

Anti-BSA = antibodies to bovine serum albumin; CMP = comprehensive metabolic panel; CBC = complete blood count w/ differential; EVENDOL = EValuation ENfant DOuLeur; FPRS = Wong-Baker Faces Pain Rating Scale; POSAS = Patient and Observer Scar Assessment Scale; PRA = panel reactive antibodies; PSAQ = Patient Scar Assessment Questionnaire.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

In this study, up to 50 subjects will be enrolled into one of two age cohorts: 2 to < 12 years (up to n = 40) and 12 to ≤ 17 years (up to n = 10). Subjects who fail to meet eligibility criteria following excision/debridement of their wound but before StrataGraft application may be replaced and a new subject number assigned.

7.1. Subject Inclusion Criteria

An included subject will be or have:

1. Aged 2 to 17 years, inclusive, as of the time of consent.
2. Written informed consent from parent(s) or legal guardian(s) and assent from the child when appropriate, as determined by the Institutional Review Board (IRB), consistent with regulatory criteria and requirements.
3. Sufficient healthy skin identified and reserved as a donor site in the event that the StrataGraft treatment site(s) requires autografting.
4. Thermal burns of no more than 30% TBSA.
5. Consenting adult(s) is/are able and willing to attend/bring child to the scheduled visits and comply with study procedures.
6. Study treatment area(s) that is/are: a) DPT in depth (ie, containing dermal elements) and for which excision and autografting are clinically indicated, as assessed by the investigator, and b) located on the torso or extremities.
7. Study treatment area of 0.5% to 10% TBSA, which may be composed of up to 3 non-contiguous areas located on the same extremity or plane of the torso.

7.2. Subject Exclusion Criteria

An excluded subject will be or have:

1. Pregnant or breastfeeding.
2. Receiving systemic immunosuppressive therapy and/or systemic corticosteroids (inhaled corticosteroids are allowed)
3. A known history of malignancy.
4. Pre-admission insulin-dependent diabetes.
5. Concurrent trauma, conditions, and/or personal situations that, in the opinion of the investigator, may compromise subject safety or the study objectives.
6. Burn injury occurred ≥ 14 days prior to StrataGraft application.
7. An expected survival of less than 12 months.
8. Participated in an interventional study of a drug, device, or biologic within the 90 days preceding enrollment.
9. Proposed study site(s) has/have been previously excised and/or autografted.

10. Proposed study site(s) are located adjacent to an unexcised burn area.
11. Proposed study site(s) demonstrate signs and symptoms of wound infection, per judgment of the clinical investigator.
12. Proposed study sites(s) lie across joints or are located on the feet (ie, distal to the malleolus), hands (distal to the wrist), face, neck, buttocks, perineum, or genitalia.

7.3. Screen Failures

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

Subjects who do not meet all of the eligibility criteria will be deemed a screen failure, and the following information will be recorded:

- Demographics (age, sex, race/ethnicity);
- Assessment of eligibility criteria;
- Reason for screen failure; and
- Any AE experienced by the subject following written, informed consent until excluded from study participation.

8. TREATMENT OF SUBJECTS

"Study treatment" is defined as the application, administration, or performance of any treatment to the study subject per this study protocol. In this study, StrataGraft (the investigational product [IP], Table 3) will be applied to the excised/debrided burn wound bed of consented subjects who meet all eligibility criteria (Section 7.1 and Section 7.2).

Table 3: Investigational Product

	StrataGraft
Dosage form:	Rectangular cellularized scaffold sheet
Unit surface area	Approximately 100 cm^2
Route of administration	Topical
Manufacturer	Stratatech Corporation, a Mallinckrodt Company

Qualified subjects will have the entire study treatment area located on the extremities and/or torso and each subject will have a sufficient area of healthy skin available for use as a donor site in the event that autografting is required. Burn areas not included as the study site will be treated per institutional standard of care.

8.1. Treatment Administration

8.1.1. Study Enrollment

Subjects will be enrolled after meeting all eligibility criteria. Any subject who fails to meet all eligibility criteria will be considered a screen failure and subsequently may not be enrolled in the study.

8.1.2. Burn Wound

Only following removal of nonviable tissue may the wound be fully assessed and a definitive determination of burn depth made. Following excision/debridement, the study area(s) will be identified and photographed prior to StrataGraft application. Subjects will receive StrataGraft treatment to 0.5% to 10% TBSA, which may be composed of up to 3 non-contiguous areas located on the same extremity or plane of the torso. Once the designated study site(s) have been excised/debrided and the subject has met all eligibility criteria, StrataGraft will be fenestrated or meshed (up to a 1:1 ratio) and secured to the wound with sutures, staples, fibrin sealant, or tissue glue and dressed with a non-adherent, porous dressing. Secondary dressings and outer wrap/immobilizing dressing will be applied per investigator discretion, barring use of any prohibited materials (see Section 8.2.2). All dressings, including the primary dressing, will be changed per institutional standards until closed, or as long as deemed clinically necessary by the investigator.

8.2. Prior and Concomitant Medications/Therapies

The start and stop date, dose, unit, frequency, route of administration, and indication for all prior (taken within the 14 days prior to Day 1) and concomitant medications (taken from Screening through the Month 12 end of study visit) will be recorded. Start and stop dates of non-drug therapies (eg, oxygen supplementation, physical therapy, etc.) administered. Dates of transfusion of transfusions of blood or blood components as well as the number of units transfused will be recorded.

At investigator discretion, treatment of infected/suspected infected wound sites may include the use of targeted wound cleansing agents, topical antimicrobial agents and/or systemic antibiotics. Study wound sites may not be treated with any prohibited therapies, as outlined in Section 8.2.2.

8.2.1. Permitted Concomitant Therapies

Subjects may continue all normally prescribed medication regimens during this study and must notify the investigator when changes are made to their medication regimens. Childhood vaccinations may continue as scheduled during study participation.

Therapies designed to optimize scar outcome may be implemented as per institutional standard of care and may include, but are not limited to, range-of-motion exercises, massage, compression, and silicone dressings. Use of these therapies will be recorded.

8.2.2. Prohibited Therapies

Starting with Screening, the following treatments are not permitted:

- Application of any silver- or sulfa-containing topical agents (including mafenide acetate) or dressings to the StrataGraft treatment site through confirmed complete wound closure.
- Use of chlorhexidine- or iodine-based skin cleansers until confirmed, complete wound closure. Such cleansers may be used for wound preparation prior to StrataGraft application and must be thoroughly rinsed off prior to placement.
- Use of any investigational drug, device, or procedure administered as part of a research study.
- Use of laser therapy to scars located on the StrataGraft treatment site through completion of the Month 12 visit.

If any prohibited therapy is administered during the study, all pertinent information will be recorded. The designated study medical monitor must be informed immediately upon discovery of such use.

8.3. Study Treatment Compliance

StrataGraft will be administered by investigator or sub-investigator(s) at the study site, and subjects will be followed to ensure compliance with wound care regimen.

8.4. Randomization and Blinding

Not applicable. This is an open-label study.

9. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

Detailed information regarding shipping, receipt, handling, storage, preparation, and accountability of IP may be found in the Manual of Procedures and are only briefly addressed in this section.

9.1. Investigational Product

The IP for this study is StrataGraft, a viable, bioengineered, allogeneic, cellularized scaffold product composed of a differentiated epidermal compartment comprising epidermal cells from a single human donor grown on a dermal equivalent composed of purified Type I animal collagen containing normal human fibroblasts from a second donor.

9.2. Investigational Product Packaging and Labeling

The IP, StrataGraft, will be provided by Stratatech Corporation and each piece will be labeled per local and national requirements.

9.3. Investigational Product Receipt and Storage

StrataGraft will be shipped to the study site on dry ice. Upon arrival at the site, StrataGraft may be maintained in the sealed shipping container until the data and time indicated on this container. If StrataGraft will not be used until after the date and time indicated on the shipping container, upon arrival at the site, StrataGraft should be transferred from the shipping container to a secure, ultra-cold (-70°C to -90°C) freezer with monitored temperature. Details regarding shipment and storage requirements can be found in the Manual of Procedures. Once StrataGraft has been received at the site, any excursion from required storage range (-70°C to -90°C) must be reported to the Sponsor as soon as the temperature fluctuation becomes known and prior to clinical use**.**

9.4. Investigational Product Preparation and Administration

StrataGraft is supplied as a rectangular cellularized sheet of approximately 100 cm^2 and is applied topically by the investigator. The necessary procedures for preparing the product for administration are provided in the Manual of Procedures.

9.5. Investigational Product Accountability

In accordance with the International Council on Harmonisation (ICH) requirements, the investigator will account for all study IP furnished to the study site. An accountability record will be maintained for this purpose. An accounting for each unit of IP provided will be maintained, noting dates of receipt and use, as well as ultimate disposition. The investigational product will be maintained under locked/secured, temperature-controlled storage conditions at the study site.

9.6. Investigational Product Handling and Disposal

See Manual of Procedures for complete instructions.

10. SCHEDULE OF STUDY EVALUATIONS

Section 6.8 contains a Table of Study Events and Assessments.

10.1. Screening

Screening assessments and baseline procedures must be completed within 14 days of injury.

The following assessments and procedures will be performed during the Screening period:

- Obtain written informed consent and subject assent, as appropriate (Section 11.1).
- Collection of medical history, including etiology of the burn injury (Section 11.2.1).
- Collection of concomitant medications (Section 11.4).
- Collection of height and body weight (Section 11.2.3).
- Abbreviated physical assessment, including assessment of vital signs (Section 11.2).
- Assessment of total burn area (% TBSA burn), depth and location(s) (Section 11.3).
- Evaluation of burn wound for signs of infection (Section 11.3.6).
- Pregnancy test for females of child-bearing potential (Section 11.2.2).
- Assess for any AEs (Section 11.9).
- Collection of clinical laboratory assessments for comprehensive metabolic panel (CMP) and complete blood count (CBC) with differential (Section 11.5), if in medical record, or collection of samples for these assessments if venipuncture performed
  - Micro collection is encouraged for all subjects weighing less than 26 kg to reduce volume of sample.

10.2. Treatment Day 1 (Day of Excision/Debridement and Investigational Product Application)

Application of StrataGraft must be completed within 14 days of injury.

The following assessments and procedures will be performed:

- Obtain vital signs (Section 11.2.4).
- Collection of concomitant medications (Section 11.4).
- Collect archival blood sample (Section 11.6).
- Collect baseline laboratory samples for CMP and CBC with differential (Section 11.5) if values were not obtained or samples not collected during Screening and within 48 hours of study treatment.
  - Micro collection is encouraged for all subjects weighing less than 26 kg to reduce volume of sample.

  - Laboratory assessments performed within 48 hours of the study procedure will be abstracted from the medical record and serve as baseline study assessments. If not available, samples will be obtained for Baseline.

- Collect baseline PRA and anti-BSA antibody samples (Section 11.6).
- Photograph the study site(s): 1) pre-excision/debridement, 2) post-excision/debridement, and 3) post-StrataGraft application. Thoroughly clean and excise/debride burn wounds (Section 11.3.4).
- Clinically assess all wounds for the presence of infection (infected wounds and wounds adjacent to an infected site may not be used as study sites) (Section 11.3.6).
- Assess wounds after excision/debridement and designate the Study treatment area of 0.5% to 10% TBSA, which may be composed of up to 3 non-contiguous areas located on the same extremity or plane of the torso. (Section 8.1.2).
- Apply StrataGraft (Section 8.1.2).
- Document number of StrataGraft constructs applied (details are provided in the Manual of Procedures).
- Assess for any AEs (Section 11.9).

10.3. Treatment Days 7, 14, and 21 (± 2 days), Day 28 (± 3 days), and Weeks 5 - 11 (± 3 days)

Subjects will be assessed weekly until complete wound closure of study treatment site(s) is/are confirmed. The following assessments or procedures will be performed at those visits:

- Obtain vital signs (Section 11.2.4).
- Remove all dressings and expose study treatment site(s). Reapply dressings, if necessary, after all wound assessments are complete.
- Photograph all study treatment site(s) (Section 11.3.4). Photographs may be taken by study site personnel, or by trained caregivers if the subject is not able to attend the study site.
- Assess each study treatment site for:

  – Signs and symptoms of infection and, if infection is suspected, assess and treat as outlined in Section 11.3.6 and Section 11.9.1.5.

  – The percent re-epithelialized of the study site until complete closure is noted (Section 11.3.2).

  – Autograft placement on study treatment site since last study visit, noting area autografted, if any; placement is assessed until complete closure is noted (Section 11.3.3).

  – Complete closure and, if closed, confirm the maintenance of closure at the next visit (Section 11.3.2). After the first observation of closure, confirmation of wound

closure will be done at a second visit at least 2 weeks after initial observation but no later than Week 20.

- Assess pain at the study treatment site(s) using the EVENDOL (observer or parent) or FPRS (subject) rating scale (Section 11.7).
- Document reason(s) for continued hospitalization if subject has not been discharged (Section 11.8).
- Update any changes to concomitant medications and/or procedures, including any readmission to hospital related to the study wound(s) or scar management measures (Section 11.4).
- Abstract from the medical record results of any safety laboratory results (ie, CBC with differential and CMP) performed since prior visit (Section 11.5). If no recorded values in medical record from Day 28 through Week 11, samples for CBC with differential and CMP may be collected during a clinically necessary venipuncture. Only 1 post-baseline sample per subject is needed.
- PRA and anti-BSA antibody samples may be collected at any visit after Week 6, but only if they may be collected during a clinically necessary venipuncture (Section 11.6). Only 1 post-baseline sample per subject is needed.
- Once closed, obtain POSAS and PSAQ assessment of study treatment site(s) (Section 11.3.5).
- Assess for any AEs (Section 11.9).

10.4. Treatment Week 12 (± 1 week) and Months 6 and 12 (± 1 month)

The following assessments or procedures will be performed:

- Obtain vital signs and measure height/length and body weight (Section 11.2.3 and Section 11.2.4).
- Remove all dressings, if any, and expose study treatment site(s). After assessments are completed, reapply dressings, if necessary.
- Photograph all study treatment site(s) until complete closure, or the study site is autografted, then photograph all study treatment sites at Week 12 and Months 6 and 12 (Section 11.3.4).
- Assess each study treatment site for:
  - Signs and symptoms of infection and, if infection is suspected, assess and treat as outlined in Section 11.3.6 and Section 11.9.1.5.
  - The percent re-epithelialized of study treatment site(s) until complete closure is noted (Section 11.3.2).
  - Autograft placement on study treatment site(s) since last study visit, noting area autografted, if any; placement is assessed until complete closure is noted (Section 11.3.3).

  - If closed, confirm the maintenance of closure of study treatment site(s) at the next visit (Section 11.3.2). After the first observation of closure, confirmation of wound closure will be done at a second visit at least 2 weeks after initial observation but no later than Week 20

- Assess pain at the treatment site(s) using the EVENDOL (observer or parent) or FPRS (subject) rating scale (Section 11.7).
- Document reason(s) for continued hospitalization if subject has not been discharged (Section 11.8).
- Update any changes to concomitant medications and/or procedures, including any readmission to hospital related to the study wound(s) or scar management measures (Section 11.4).
- Obtain POSAS and PSAQ assessment of study treatment site(s) (Section 11.3.5).
- PRA and anti-BSA antibody samples may be collected at any visit after Week 6, but only if they may be collected during a clinically necessary venipuncture (Section 11.6). Only 1 post-baseline sample per subject is needed.
- Assess for any AEs (Section 11.9).

11. STUDY ASSESSMENTS AND PROCEDURES

All study assessments and times are listed in the Schedule of Study Events (Section 6.8). General instructions for the administration of these assessments are provided in the following subsections. Additional (unscheduled) safety assessments may be performed as needed. Specific instructions and questionnaires/forms (where appropriate) will be provided in a study manual. All assessments will be recorded in the electronic case report form (eCRF).

It is expected the subjects will attend all scheduled study visits. Should a subject be unable to participate in an in-person visit, wound assessments and solicitation of AEs may be performed by telemedicine/video interactions. However, no assessment of wound re-epithelialization nor observation or confirmation of closure may be performed via video/telemedicine visits. These wound assessments may be performed only during a face-to-face visit.

11.1. Informed Consent/Assent

The parents and/or guardians of minor children must provide written consent for the participation of their child/ward in this study prior to any study assessment. Only informed consent forms reviewed and approved by the IRB of record may be used.

Minor children will be assessed for their level of comprehension and involved in the consent process as appropriate. For purposes of this study, assent to participate will be obtained from the child, when appropriate, as determined by the IRB, and consistent with regulatory criteria and requirements.

Subjects who reach the age of majority (usually 18 years of age) during their participation in the study will be re-consented.

11.2. Screening Assessments

The screening period is a maximum of 14 days from the day of injury to Day 1. The screening assessments will help to determine eligibility for study enrollment. During this period, the prospective study sites will be managed nonoperatively per the institution’s standard of care.

Subjects and/or parent/guardian will provide informed consent prior to any study-specific assessments being performed. If, following excision/debridement, the designated potential study site does not meet eligibility criteria, the subject will be considered a screen failure and no further assessments or study procedures will be performed. Only after excision/debridement of the study site and application of StrataGraft will the subject be considered “enrolled.”

11.2.1. Medical History and Physical Examination

Significant medical history will be collected using an abbreviated review of systems with particular attention to any previous surgical procedures performed, hospitalizations, diagnosed chronic conditions and any routinely administered medications. The date of last menstrual period will be collected from post-menarche females.

The physical examination will be performed to include evaluation of lungs, heart, abdomen, and extremities. The findings of the physical examination will be recorded.

Finally, background on the injury itself, including the date of the burn, date of first hospitalization, and etiology of the burn will be collected.

11.2.2. Pregnancy Test

A pregnancy test will be conducted for females of child-bearing potential. Results must be available prior to Day 1. Subjects with positive results at Screening are excluded from participation in this study. Serum testing is preferred, but urine testing is acceptable.

If applicable, the subject's agreement to use contraception throughout their study participation will be documented (see Appendix 3).

11.2.3. Height and Body Weight

The screening height and body weight measurements will be used to calculate body surface area. Height and body weight will be obtained at certain study visits as indicated in the Schedule of Study Events (Section 6.8).

11.2.4. Vital Signs

Vital signs will be obtained with the subject at rest and will include systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature. The results, date, and time for all vital sign assessments will be recorded. Any change from the Screening vital signs that is considered clinically significant by the investigator will be recorded as an AE.

11.3. Study Site Assessments

11.3.1. StrataGraft Application

On Day 1, following excision/debridement of study burn wound(s), the treatment site(s) will be identified and following fenestration/meshing, sheet(s) of StrataGraft will be applied and secured. The number of StrataGraft constructs applied to each treatment site will be documented. Details are provided in the Manual of Procedures.

11.3.2. Wound Closure Assessment

After excision/debridement and application of study treatments, the investigator will examine the study site(s) as per the Schedule of Study Events (Section 6.8) and visually assess wound closure, documenting a quantitative assessment of the proportion of the wound that is re-epithelialized. For this study, confirmed complete wound closure is defined as, "complete re-epithelialization of the wound without drainage" observed at 2 consecutive visits at least 2 weeks apart (FDA, 2006), but no later than Week 20.

11.3.3. Area of the Study Sites Autografted

The area of each StrataGraft treatment site that is autografted will be measured during the autografting procedure. Details about obtaining wound measurements is provided in the Manual of Procedures.

11.3.4. Photography of Treatment Sites

All StrataGraft treated sites will be photographed in the operating room and at each study visit to serially assess the area(s) of open wound in each treatment site. The photographer will be a trained study team member or trained caregiver. Subjects will attend weekly visits until complete wound closure is confirmed. Following confirmed complete wound closure, or if subjects cannot attend the study site, subjects and/or caregivers will be asked to photograph their wounds so that ongoing closure of their wound(s) can be assessed. In the event of a wound-related adverse event, photos of the affected wound will be taken to help document the event. Specific instructions and guidelines for photo-documentation will be provided in the Photography Manual.

11.3.5. Skin Quality of Treatment Sites

The POSAS (Patient Observer Scar Assessment Scale) will be used to assess the StrataGraft treated site(s) at visits designated in the Schedule of Study Events (Section 6.8). The POSAS scale has 2 components: the observer assessment and the subject assessment. The observer assessment uses a 10-point scale to assess vascularity, pigmentation, thickness, height, pliability, surface area, and overall opinion, while the subject component uses the same 10-point scale to assess pain, itching, stiffness, color, thickness, and overall opinion of StrataGraft treated sites. The investigator will complete the Observer POSAS assessment and a parent/guardian will complete the subject assessment on behalf of subjects unable to do so themselves.

The PSAQ (Patient Scar Assessment Questionnaire) was created specifically to assess linear scars and has not previously been used to assess burn scars. However, one of the 5 subscales within the tool is a subjective assessment of a subject's satisfaction with their scar, an assessment that is not made in the POSAS. In its development, the PSAQ demonstrated internal consistency for each subscale, including the Satisfaction with Appearance subscale (Cronbach α of 0.89 to 0.94), as well as high test-retest reliability (intraclass correlation coefficient [ICC] of 0.67 to -0.83) of the same, demonstrating a high level of reliability in the use of the subscales independently. Only the 9 items of the Satisfaction with Appearance subscale will be completed by the subject or a parent/guardian (on behalf of subjects unable to do so themselves) at each assessment per the Schedule of Study Events (Section 6.8).

11.3.6. Other Wound Assessments

The StrataGraft treatment site(s) will also be assessed for clinical signs of infection, and the investigator will document the appearance of the wound using various descriptive terms. At investigator discretion, treatment of infected/suspected infected wound sites may include the use of targeted wound cleansing agents, topical antimicrobial agents (excluding silver and sulfa- -containing treatments such as mafenide acetate) and/or systemic antibiotics. Wound-related adverse events will be documented with photographs of the affected wound. See Section 11.9.1.5 for further details.

11.4. Concomitant Medications and Procedures

The start and stop dates, dose, unit, frequency, route of administration, and indication for all prior and concomitant medications, nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) and other procedures will be recorded in the eCRF.

11.5. Safety Laboratory Tests

Results of CMP and CBC with differential, collected for clinical purposes, will be abstracted from the medical record. If such results are not available, blood samples for research purposes will be collected only as part of a clinically necessary venipuncture. Clinical sample analysis for CMP and CBC with differential studies will be performed at the institution's local laboratory.

Investigators must review and sign laboratory reports and document the clinical significance of any laboratory abnormalities. New, clinically significant laboratory abnormalities or clinically significant changes in laboratory values will be reported as AEs.

11.6. Immunological Assays and Archival Samples

Panel reactive antibodies (PRA), anti-BSA antibody and archival samples will be obtained prior to StrataGraft application from all enrolled subjects. Samples for the assessment of PRA and anti-BSA antibodies will also be obtained between Week 7 and Month 6 for all treated subjects.

Specific instructions for collection, processing, storage, and shipment of these samples will be provided in the Laboratory Manual.

11.7. Pain Assessment

The EVENDOL pain assessment scale, a tool validated in preverbal children, will be used to assess pain in enrolled subjects up to 5 years of age (inclusive). The EVENDOL scale is designed such that it can be completed by an observer (eg, parent) based upon outward behavioral manifestations such as crying, facial expressions, movements and posturing as well as environmental interactions (Fournier-Charrière, 2012).

The FPRS (FACES pain rating scale), a well-documented and validated tool, will be used to assess pain in enrolled subjects older than 5 years of age. The FPRS is demonstrated to effectively evaluate pain using a Likert-like scale of facial expressions, which are converted into numeric values to obtain a quantitative assessment of pain (Wong, 1998).

Details regarding administration of the pain assessment tools are provided in the Manual of Procedures.

11.8. Assessment of the Need for Continued Hospitalization

At each study visit subsequent to Day 1 but prior to hospital discharge, an assessment of the need for continued hospitalization will be completed. Investigators will be asked to identify the reason(s) for continued hospitalization including: pain management, fluid or nutritional status, infection risk, ongoing infection, inability to perform activities of daily living, insufficient social support, or other issues.

11.9. Adverse Events and Serious Adverse Events

11.9.1. Definitions

11.9.1.1. Adverse Event (AE)

An AE is any untoward or undesirable medical occurrence in a subject who is administered a study treatment, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Examples of AEs include but are not limited to:

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

Events that do **not** meet the definition of an adverse events include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Failure to achieve complete wound closure by Week 12.

11.9.1.2. Unexpected Adverse Event

An unexpected AE is an AE which exhibits a different nature or severity than those identified in the Investigator's Brochure or has not previously been noted in relationship to StrataGraft.

11.9.1.3. Treatment Emergent Adverse Events

Treatment-emergent AEs are defined as those that are not present at start of study treatment or that represent the exacerbation of a pre-existing condition during the treatment-emergent period. The treatment-emergent period is defined as the time from the application of StrataGraft to the end of the study.

11.9.1.4. Serious Adverse Event (SAE)

An SAE is defined as any untoward medical occurrence that results in any of the following outcomes:

Death

Death is an outcome of an event. The cause of death should be recorded and reported on the SAE Form. All causes 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. See Section 4.4 for xenotransplantation considerations.

Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Inpatient hospitalization or prolongation of existing hospitalization

Hospitalization is defined as an admission to a hospital. The following situations should not be reported as SAEs:

- A hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.

- A hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (eg, stent removal after surgery). This should be recorded in the study file.
- A hospitalization for a pre-existing condition that has not worsened.

Persistent or significant incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Congenital anomaly or birth defect

After enrollment and follow up in this study, any pregnancy reported to occur will be followed to conclusion and all live-born children will be followed for 28 days following birth. Any congenital anomaly or birth defect will be reported.

Important Medical Events

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, may jeopardize the subject or the subject may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Anticipated Adverse Events

Adverse events (serious or nonserious) that commonly occur in the study population or background regimen will be considered anticipated events. Such events include known consequences of the condition under investigation (eg, symptoms, disease progression) and other events that may be common in this study population. A list of anticipated events for this study population is provided in the Investigators Brochure. Anticipated events are to be recorded in the eCRF and reported as SAEs when serious. These SAEs will not be expedited to health authorities, but rather, included in aggregate safety reports.

11.9.1.5. Adverse Event of Special Interest

An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. AESI will be reported using the SAE/AESI Report Form and observe the same reporting timeline (Table 6). For this study, Adverse Events of Special Interest (AESI) include:

- Signs/symptoms of endotoxin reaction (ie., combination of hypo/hyperpyrexia, hypo/hypertension, tachycardia, tachypnea, and change in mental status) within 24 hours after StrataGraft application
- Unexpected or unusual infections
- Dermatological malignancy

If any of the above occurs, the event will be reported within 24 hours of first knowledge of the event and follow-up reports provided as changes in the event occur. Photographs will be taken of the affected wound(s) to document the AESI.

11.9.2. Adverse Event Medical Management Plan

In the event of an AE, the investigator will use accepted standard of care (medication or surgery) as needed. A tiered approach will be used for the medical management of complications specific to the study burn sites, as described below:

- Initial management of local infection or immune reactions with topical antimicrobials or anti-inflammatory agents, respectively.
- Systemic antibiotics or anti-inflammatory medications administered for infections or immunological responses that fail to respond to topical therapy.
- For complications that do not respond to topical or systemic therapy, the treated wound may be excised and the complication managed with topical or systemic therapy, as necessary.
- Based on clinical judgment, autograft may be applied to the resulting wound bed to expedite wound closure.

11.10. Relationship to Investigational Product

The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.

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

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

The following classifications should be used when evaluating the relationship of AEs or SAEs to study treatment.

Table 4: Adverse Event Relationships

Relationship	Definition
Unrelated	No relationship between the AE and the administration of study treatment; the AE can be explained by other etiologies such as concomitant medications or subject's clinical state.

Relationship	Definition
Possibly related	A reaction that follows a plausible temporal sequence from administration of the study treatment, has a biologically causal relationship with the study treatment, or for which an alternative explanation for the AE is lacking. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Probably related	A reaction that follows a plausible temporal sequence from administration of the study treatment and has a biologically causal relationship with the study treatment, and the influence of alternative factors for the AE is unlikely.

11.11. Severity Assessment

For purposes of consistency, if required the investigator may use the intensity grades presented in Table 5.

Table 5: Adverse Event Intensity Grades

Grade	Definition
Mild	Does not interfere with subject's usual function and activities.
Moderate	Interferes to some extent with subject's usual function and activities.
Severe	Interferes significantly with subject's usual function and activities.

To ensure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided:

The term "severe" is used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). The event itself, however, may be of relatively minor medical importance (such as a severe headache). This is not the same as "serious," which is based on the subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

If an AE increases in severity (eg, from moderate to severe); decreases in severity (eg, changes from moderate to mild); or if there is a change in seriousness, a new AE will be opened and the original AE will be closed. If an AE is still ongoing at the time of a subject's completion of the last study follow-up visit, the resolution/stop date and time is left blank.

11.12. Recording and Reporting Adverse Events

Adverse events will be recorded starting at the signing of the informed consent form (ICF) and will be followed by the investigator until the AE is resolved or stabilized. All study site follow-up should be documented.

Adverse events, AESIs, and SAEs will be reported from execution of the ICF through completion of study participation. The investigator is required to record the AE, regardless of the severity of the event or its relationship to study treatment.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

The investigator must follow all AEs until the event has resolved or stabilized or at such time, the investigator refers the subject to a non-study physician. The investigator will document further all of the follow-up information in the subject's source documents.

The investigator is responsible for reporting all AEs as presented in Table 6.

Table 6: Reporting Requirements for Adverse Events

Category	Reporting Time	Type of Report
Serious adverse events, and AESIs	Within 24 hours of first knowledge of event	Initial report on the SAE/AESI Form, appropriate eCRF, and source document
	Within 24 hours of receipt of follow-up information	Follow up report on the Follow-up SAE/AESI Form, appropriate eCRF, and source document
Nonserious adverse events	Per case report form submission procedure	Appropriate eCRF and source document

AESI = adverse event of special interest; eCRF = electronic case report form; SAE = serious adverse event.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the SAE report form.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to an agency.

11.13. Pregnancy Reporting

If a female subject, or the female partner of a male subject, becomes pregnant during the study, the investigator will report to the Sponsor as soon as she/he becomes knowledgeable of the pregnancy. The subject will be followed for the duration of the pregnancy and the outcome (eg, spontaneous abortion, live birth, still birth, congenital anomalies, birth defects) will be reported to the Sponsor as soon as it is known. If the pregnancy results in a live birth, a postdelivery follow-up will be performed at least 28 days after the baby is born and must be reported to the Sponsor's pharmacovigilance personnel, or designee, within 24 hours of the study site becoming aware of the follow-up information.

Information including the definition of Woman of Childbearing Potential (WOCBP), Contraceptive Guidance, and Collection of Pregnancy Information can be found in Appendix 3.

12. STATISTICAL CONSIDERATIONS

12.1. Sample Size Determination

Approximately 50 subjects will be enrolled into one of two age cohorts: up to 40 subjects in 2 to ≤12 years cohort or up to 10 subjects in 12 to ≤17 years.

An overall sample size of 50 subjects will provide greater than 90% power to determine that at least 50% of the subjects achieve confirmed complete closure of all StrataGraft treatment sites on or before Week 12 without autograft placement, assuming that the actual proportion of subjects with confirmed complete closure of all StrataGraft treatment sites without autografting will be ≥ 83%. This assumption is based upon the results of a study in adults for the same indication (Holmes, 2020).

Similar power is provided with the 40-subject sample of the 2 to ≤12 years cohort, which is considered to be the more common group to be enrolled. In the event that the 40 subjects have been enrolled into the 2 to ≤12 years cohort but the enrollment into the older 12 to ≤17 years cohort is not yet complete, the Sponsor reserves the right to close the study at their discretion.

12.2. Analysis Populations

The Intent-to-Treat (ITT) and Safety populations will include all enrolled subjects who received StrataGraft.

12.3. Statistical Analyses

This section provides a general summary of the statistical methods to be used in analyzing study data. A more detailed statistical analysis plan (SAP) will be provided in a separate document that will be finalized prior to database lock. SAS version 9.4 or newer will be used.

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.

12.3.1. Efficacy Analyses

12.3.1.1. Primary Endpoint

The pediatric study plans to enroll up to 50 subjects into two age cohorts: 2 to ≤ 12 years and 12 to ≤ 17 years. Endpoints will be assessed using the entire ITT population.

The primary efficacy endpoint for this study the percentage of subjects achieving confirmed complete closure of all StrataGraft treatment sites on or before Week 12 without autograft placement. For subjects with more than one treatment site, all treatment sites must be confirmed closed before the subject can be declared to be confirmed closed. Confirmed complete wound closure is defined as complete skin re-epithelialization confirmed at 2 consecutive visits at least 2 weeks apart but no later than Week 20. Complete confirmed wound closure will be considered to have occurred at the earlier of the two observations of complete skin re-epithelialization without drainage.

For the primary efficacy endpoint, number (%) and 95% Confidence Interval (CI) derived from the normal approximation to the binomial will be summarized based on the ITT population. Subjects with missing data will be imputed as non-responders. The statistical significance for the primary endpoint is declared if the lower limit of the 95% CI of the endpoint is ≥ 50%.

The analysis will also be performed based on all observed data, i.e, excluding any missing data. The analyses by age cohort will be presented.

The Objective, Population, Hypothesis, Endpoint, and Intercurrent Events and Data Handling for the Primary Endpoint are described in Table 7.

12.3.1.2. Ranked Secondary Endpoints

After the primary endpoint is successfully reached, the ranked secondary efficacy endpoints will each be tested with a 2-sided confidence interval with 0.05 Type I error in a hierarchical manner in the rank order as in Table 8. The ranked secondary endpoints are:

1. Mean of averaged percent area of StrataGraft treatment site closed per subject at Week 12 without autograft placement
2. Number (%) of confirmed complete wound closures of the StrataGraft treatment sites on or before Week 12 without autograft placement
3. Mean of averaged percent area of StrataGraft treatment site autografted by Week 12

For continuous efficacy endpoints, missing data will not be imputed. Missing or incomplete binary variables will be imputed as failures. Missing data are anticipated to occur only if the subject is lost to follow-up because information can be obtained for a missing visit when the subject returns for a subsequent visit. If a subject has autograft placement, the data collected after the autograft placement will be censored.

The averaged percent area closed per subject at Week 12 will be calculated as (Sum of percent area closed across treatment sites for a subject at Week 12/the total number of treatment sites on a subject).

The percentage of StrataGraft treatment sites with confirmed complete wound closure on or before Week 12 will be calculated as [(Total number of StrataGraft treatment sites with confirmed complete wound closure without autografting on or before Week 12/Total number of treatment sites) x 100].

The averaged percent area of StrataGraft treatment sites per subject autografted by Week 12 will be calculated as (Sum of percent area of StrataGraft treatment sites per subject autografted by Week 12/the number of treatment sites on that subject). It is a cumulative sum of percent area autografted for all nonmissing visits on or before Week 12.

The summary statistics with 95% confidence interval (CI) and p-value based on null hypothesis specified in Table 8 for each endpoint from t-distribution will be presented based on the ITT population by designated treatment site and pooled designated treatment site. The analyses by age cohort will be presented.

12.3.1.3. Binary Endpoints

For binary endpoints, number (%) of subjects and its 95% CI derived from the normal approximation to the binomial will be summarized based on ITT by designated treatment site and pooled designated treatment site. The denominator for a treatment site is determined by numbers of subjects with the designated site. The number and percent of missing data will be shown.

The missing data of binary endpoints will not be imputed for exploratory endpoints.

12.3.1.4. Exploratory Endpoints

For continuous and binary exploratory endpoints, the analyses will be the same as ones in Section 12.3.1.2 and Section 12.3.1.3. For the time-to-event efficacy endpoint, the Kaplan-Meier curves will be presented based on the ITT population. Subjects not having any event during the study will have their time censored at the last available date in the study. The Kaplan-Meier estimates and 95% CIs for the 25th percentile, 50th percentile and 75th percentile will be presented.

For each exploratory continuous endpoint, the summary statistics with 95% confidence interval (CI) will be presented based on the ITT population by designated treatment site and pooled designated treatment site.

The exploratory endpoints for this study are:

- Mean percent area of StrataGraft treatment site closed without autograft placement at Week 8
- Mean Patient and Observer Scar Assessment Scale (POSAS) observer total score at Week 12, and Months 6 and 12.
- Changes in skin quality outcome (POSAS and Patient Scar Assessment Questionnaire [PSAQ] scores) across time.
- Incidence and severity of pain at the treatment site using EVENDOL (EValuation ENfant DOuLeur, ie, Evaluation of Child Pain; observer or parent) or FPRS (Wong-Baker Faces Pain Rating Scale with 6 faces with expressions denoting degrees of pain; subject) over time.
- Percent of subjects with complete closure of StrataGraft treatment site without autografting at Weeks 6 and 8 and Months 6 and 12.
- Time to complete closure following application of StrataGraft.
- Mean percent wound closure over time from Day 21 through Month 12.
- Percent of subjects achieving and maintaining persistent wound closure at Months 6 and 12.
- Mean scar satisfaction based on PSAQ scores at Week 12 and Months 6 and 12.

Table 7: The Objective, Population, Hypothesis, Endpoint and Intercurrent Events and Data Handling for the Primary Endpoint

Objective	Population	Hypothesis	Endpoint	Intercurrent Events and Data Handling
To evaluate whether StrataGraft treatment eliminates or reduces the need for autografting and promotes wound closure in a pediatric population with thermal burns that contain intact dermal elements and for which autografting is clinically indicated.	All enrolled subjects who received StrataGraft	H_0: The response rate of primary endpoint is less than or equal to the 50% H_1: The response rate of the primary endpoint is greater than the 50% Positive study criteria: The lower bound of primary endpoint 95% CI derived from the normal approximation to the binomial > 50%.	Percentage of subjects achieving confirmed complete closure of all StrataGraft treatment sites on or before Week 12 without autograft placement. Confirmed complete wound closure is defined as 100% re-epithelialization confirmed at 2 visits at least 2 weeks apart but before Week 20.	Early discontinuation due to: • Withdrawal of informed consent • Lost to follow-up • Adverse event • Investigator decision • Death • Other Missing/incomplete data will be imputed as failure (ie, no confirmed complete wound closure).

CI = Confidence Interval; LB = Lower Bound

Table 8: The Objective, Population, Hypotheses, Endpoints and Intercurrent Events and Data Handling for Ranked Secondary Efficacy Endpoints

Objectives	Population	Hypotheses	Endpoints	Intercurrent events and data handling
To evaluate the mean averaged percent of wound area closure of StrataGraft treatment site without autograft placement at Week 12	All enrolled subjects who received StrataGraft	H_{01}: Mean of averaged percent wound area closure of StrataGraft treatment site without autograft placement at Week 12 ≤ 50% H_{11}: Mean percent of wound area closure of StrataGraft treatment site without autograft placement at Week 12 > 50%	Mean of averaged percent area of StrataGraft treatment site closed without autograft placement at Week 12	Early discontinuation due to: • Withdrawal of informed consent • Lost to follow-up • Adverse event • Investigator decision • Death • Other Missing/incomplete continuous variables will not be imputed. Missing/incomplete binary variable will be imputed as failure.
To evaluate the number (%) of StrataGraft treatment sites with confirmed complete wound closure without autograft placement on or before Week 12	All enrolled subjects who received StrataGraft	H_{02}: The response rate of StrataGraft treatment sites with confirmed complete wound closure without autograft placement on or before Week 12 is less than or equal to the 50% H_{12}: The response rate of StrataGraft treatment Sites with confirmed complete wound closure without autograft placement on or before Week 12 is greater than the 50%	Number (%) of StrataGraft treatment sites with confirmed complete wound closure without autograft placement on or before Week 12	

Objectives	**Population**	**Hypotheses**	**Endpoints**	**Intercurrent events and data handling**
To evaluate the mean averaged percent area of StrataGraft treatment sites autografted per subject by Week 12	All enrolled subjects who received StrataGraft	H_{02}: Mean of averaged percent area of StrataGraft treatment sites autografted per subject by Week 12 >50%. H_{12}: Mean of averaged percent area of StrataGraft treatment sites autografted per subject by Week 12 <50%.	Mean of averaged percent area of StrataGraft treatment sites per subject autografted by Week 12	

12.3.2. Safety Analyses

All subjects who receive StrataGraft treatment will be included in the safety analyses.

AEs will be coded using the Medical Dictionary for Regulatory Activities coding classifications and presented by preferred term within system organ class. The number of AEs and the number of subjects reporting AEs will be listed and summarized descriptively by body system, preferred term, severity, and causality by designed StrataGraft (SG) treatment site, and pooled SG designated treatment sites, non-SG burn site, donor site, another site and pooled for all sites. All SAEs will be summarized and narratives will be created as appropriate.

12.3.3. Handling of Missing Data

Subjects will be encouraged to return to clinic for each scheduled visit. Direct observation of the wound and collection of data at scheduled times is essential to ensure the quality of the data. However, should a visit be missed, thereby resulting in missing data for that visit, the following approaches will be employed to manage the missing data.

For the primary efficacy endpoint, missing/incomplete data will be imputed as failure (ie, no confirmed complete wound closure).

For the ranked secondary endpoints, missing/incomplete data will not be imputed.

A full description of missing data imputation methods for all endpoints will be described in detail in the SAP.

13. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The study will be conducted in full compliance with applicable international, national, and local regulatory requirements, including US Food and Drug Administration (FDA) regulations, 21 Code of Federal Regulations (CFR) Parts 56, 314.106 and 312.120 (where applicable), International Council on Harmonization (ICH) guidelines for Good Clinical Practice (GCP) in accordance with the ethical principles that have their origins in the Declaration of Helsinki, and European regulation 536/2014/EU (where applicable).

13.1. Institutional Review Board (IRB)

It is the responsibility of the investigator to obtain the approval of the IRB/independent ethics committee (IEC) before the start of the study. A copy of the approval letter along with a roster of IRB/IEC members and compliance letter or their US Department of Health and Human Services general assurance number will be provided to the Sponsor and retained as part of the study records. During the course of the study, the investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study at appropriate intervals and at the completion of the study. The investigator will notify the IRB/IEC of SAEs or other significant safety findings per IRB/IEC guidelines. The study protocol, ICF, advertisements (if any), subject-facing materials, and amendments (if any) will be approved by the IRB/IEC in conformance with international, national, and local regulatory requirements.

An investigator may not make any changes in the conduct of the study without IRB/IEC and Sponsor approval except when necessary to eliminate apparent immediate hazards to the subjects. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately; however, the change must then be documented, reported to the IRB/IEC and Sponsor within 5 working days, who will then submit the deviation to the appropriate regulatory agency in the required time frame, if appropriate.

13.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, as requested by the Sponsor, in order to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing updated information on financial interests periodically, as appropriate.

13.3. Subject Information and Consent

The ICF to be submitted to the IRB/IEC must be reviewed and approved by the Sponsor prior to IRB/IEC submission. Once approved, only the IRB/IEC-reviewed and -approved consent form may be used to consent subjects. The investigator will provide the Sponsor with a copy of the IRB/IEC's written approval as well as the IRB/IEC-approved ICF prior to the start of the study.

At Screening, and at any other time as may be required by the study, subjects/parents/guardians will be presented with the IRB/IEC-approved consent forms and any privacy authorization as required by local and national regulations (such as the Health Insurance Portability and Accountability Act [HIPAA] authorization form). Subjects/parents/guardians will be given a description of the study providing content as per the essential elements of informed consent,

allowed time to ask questions, asked to read the consent form(s) and then provided an opportunity to discuss the contents of these forms with study site personnel.

As the subjects in this study are all minors at study enrollment, parents/guardians will be asked to sign these forms in compliance with ICH GCP and all applicable national and international regulations, before participating in any study-related procedures. Subjects and/or parent/guardian will be made aware that they may withdraw from the study at any time. Subjects unable to give written informed consent must orally assent to the procedures when having reached the appropriate age per local policies and written informed consent must be obtained in accordance with national and local laws, as applicable. Subjects who reach the age of majority (usually 18 years of age) during their participation in the study will be re-consented.

The ICF must contain all applicable elements of informed consent and the mandatory statements as defined by national and local regulations, including confidentiality. All versions of each subject's signed ICF (originals) will be maintained by the site. Copies of the signed copies of the consent form(s) and the HIPAA authorization form, if applicable, will be given to the subject/parents/guardians.

If a subject withdraws consent and/or HIPAA authorization, the investigator may no longer disclose health information, unless it is needed to preserve the scientific integrity of the study.

13.4. Master Identification List

At the time of consent, each subject will be assigned a unique study identification number. The investigator or designee is responsible for maintaining a list of each subject’s name, medical record number and assigned study identification number. The investigator must follow all applicable privacy laws in order to protect a subject’s privacy and confidentiality. Information that could identify a subject will be blinded on any material received by the Sponsor.

13.5. Data Protection

Study subjects will be assigned a unique study identifier. All subject records or datasets that are transferred to the Sponsor will be identified by this unique study identifier only. Study site personnel are responsible for purging subject names and medical record number from any records shared with the Sponsor.

Within the ICF, the subject/parents/guardians will be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection laws. In addition, subject/parents/guardians will be informed that medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by IRB/IEC members, and/or by inspectors/auditors from regulatory authorities.

13.6. Committees Structure

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

13.7. Dissemination of Clinical Study Data

Study results and de-identified individual subject data will be released as required by local and/or national regulation.

13.8. Data Quality Assurance

The Sponsor performs quality control and assurance checks on all clinical studies that it financially supports. Before enrolling any subjects in this study, Sponsor personnel and the investigator review the protocol, the investigator's Brochure, the eCRF and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study.

The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to original source data and documents.

Each subject's eCRF should be fully completed in a timely fashion, usually within 5 business days.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the Sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

Any changes in investigator(s) or sub-investigator(s) will be promptly disclosed to the Sponsor and will require an updated Statement of Investigator (ie, FDA form 1572). As such, the investigator must promptly disclose these changes to the Sponsor or their designee.

The investigator must notify their IRB/IEC of protocol deviations in accordance with local regulatory and IRB/IEC requirements.

The eCRF data are stored in a database and processed electronically. The Sponsor's medical monitor will review the data for safety information. The data are also reviewed for completeness and logical consistency. Automated validation programs will identify missing data, out-of-range data, and other data inconsistencies. In addition, clinical laboratory data will be processed electronically. Requests for data clarification will be forwarded to the study site for resolution and responded to in a timely fashion, usually within 5 business days.

13.9. Source Documents

All subject information recorded in the eCRF will be attributable to source data from the investigational site.

The investigator shall retain and preserve 1 copy of all data collected or databases generated in the course of the study, specifically including but not limited to those defined by GCP as essential. Essential documents should be retained until at least 2 years after the last approval of a marketing application or supplement in an ICH region and until there are no pending or contemplated marketing applications or supplements in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need

to be retained. Prior to destruction of any study essential documents, the investigator must first obtain written approval from the Sponsor.

13.10. Study and Site Closure

The Sponsor may suspend or terminate the study or part of the study at any time for any reason. If the investigator suspends or terminates the study, the investigator will promptly inform the Sponsor and the IRB/IEC and provide them with a detailed written explanation. Upon study completion, the investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final documents, reports, and summaries as required by regulations. Study termination and follow-up will be performed in compliance with the Sponsor's or designee's standard operating procedures.

The Sponsor, investigator, or local and national regulatory authorities may discover conditions during the study that indicate that the study or study site should be terminated. This action may be taken after appropriate consultation between the Sponsor and investigator. Conditions that may warrant termination of the study/study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- The decision on the part of the Sponsor to suspend or discontinue testing or evaluation of the investigational product.
- Failure of the investigator to enroll subjects into the study at an acceptable rate.
- Failure of the investigator to comply with pertinent regulations.
- Submission of knowingly false information from the study site to the Sponsor, study monitor, or local and national regulatory authorities.
- Insufficient adherence to protocol requirements.

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APPENDIX 1. CLINICAL LABORATORY TESTS

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

eCRF = electronic case report form; RBC = red blood cell(s); WBC = white blood cell(s); MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin

APPENDIX 2. STUDY GOVERNANCE CONSIDERATIONS

Ethical Considerations

As the pediatric population is considered a highly vulnerable group of patients, based on age and inability to give full informed consent, it is important to address the ethics of clinical research in this group. Although the FDA has mandated that a pediatric program be initiated when a treatment is relevant to this population, nonetheless, some argue it is totally unethical for children to participate in clinical studies and become the human equivalent of a test animal (Ward, 2018), which prompts this discussion for the study of StrataGraft.

There are several questions that should be addressed to justify this clinical study. These questions are: 1) is this disease only found in pediatric patients? 2) are alternate treatments available that are just as effective? and 3) will the study result in value to the subject or to the population of subjects that may receive the treatment?

To address the first question, although burns of the nature to be recruited in this study, are seen across the age spectrum, the healing response may differ depending upon the recuperative abilities, which do not change with age. As such, the issue of burn treatment in this age group is unique. Second, there are alternate treatments that may be considered to be just as effective. However, there are collateral concerns about autografting that make the StrataGraft approach particularly attractive in this population. Should StrataGraft decrease or eliminate the need for autografting in pediatric children with DPT burns as it has been demonstrated to do in adults, then use of StrataGraft may be beneficial to these patients. Moreover, the ease of use of StrataGraft will be very helpful to hospitals and medical centers in isolated areas of the United States where dedicated burn units are geographically distant.

This study will be conducted in accordance with the protocol and the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

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

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant (who is capable of providing assent) and his/her legally authorized representative and answer all questions regarding the study. Participants and their legally authorized representative must be informed that their participation is voluntary. The statement of informed consent (ICF) that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center must be signed by the subject's legally authorized representative as all subjects will be minors at the time of enrollment. Subjects who reach the age of majority (usually 18 years of age) during their participation in the study will be re-consented.
- The medical record of each study subject must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant and the participant's legally authorized representative.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Committees Structure

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

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- All records, source documents, study worksheets, signed ICFs, and any other documents pertaining to the conduct of this study must be retained by the investigator

for at least 2 years after study completion or approval of the drug, whichever comes last, unless local regulations or institutional policies require a longer retention period. (US 21CFR§312.62). No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

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

Study and Site Closure

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

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

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

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

APPENDIX 3. CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Woman of Childbearing Potential (WOCBP)

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

Non-WOCBP Status

- Premenarchal
- Permanently sterile female is a post-menarchal, pre-menopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

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

Pregnancy Testing

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

Contraception

Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, injections), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), and abstinence.

Collection of Pregnancy Information

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated

delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study, pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will continue with all scheduled study evaluations. Pregnant subjects will be followed until post-partum and the outcome of the pregnancy will be reported.

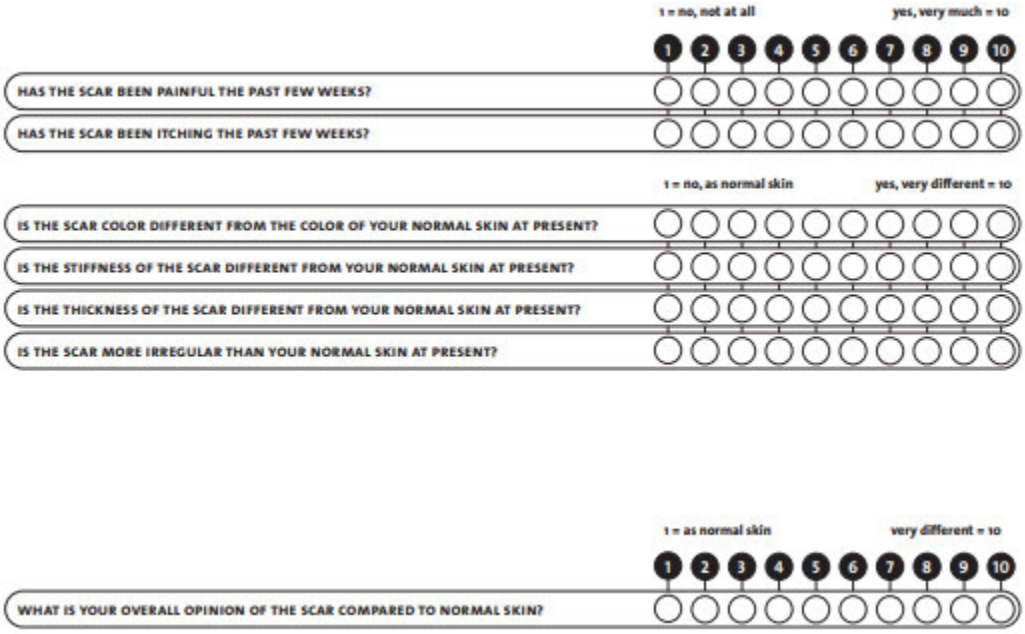
APPENDIX 4. COUNTRY-SPECIFIC REQUIREMENTS

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

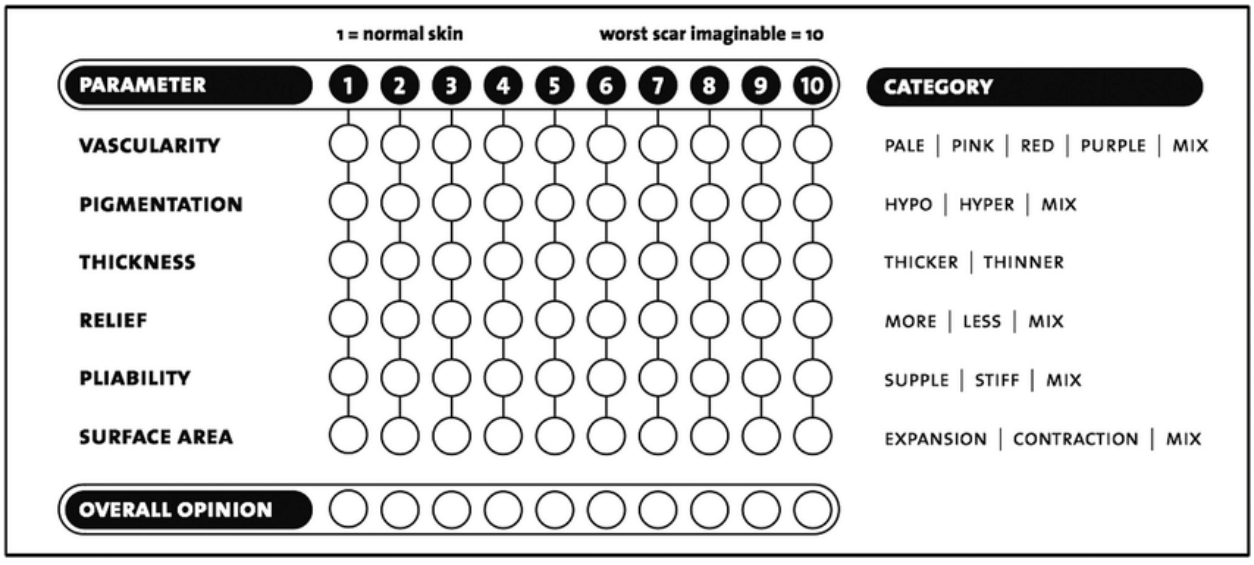
APPENDIX 5. TOOLS USED FOR ASSESSMENT DURING THE STUDY

Patient and Observer Scar Assessment Scale

Patient Scale:



Observer Scale:



Patient Satisfaction Assessment Questionnaire: Satisfaction with Appearance subscale

SATISFACTION WITH APPEARANCE

Subject ID: _____ Date of Completion: DD/MMM/YYYY Site: ☐ A ☐ B

Visit: ☐ Day 28 ☐ Month 2 ☐ Month 3 ☐ Month 6 ☐ Month 12

Read each question carefully and tick the box that most closely describes your level of satisfaction with each of the attributes of your scar.

Question	Satisfaction			
	Very Satisfied	Satisfied	Dissatisfied	Very Dissatisfied
How satisfied are you with the way the color of your scar matches with surrounding skin?	☐	☐	☐	☐
How satisfied are you with the redness of your scar?	☐	☐	☐	☐
How satisfied are you with the length of your scar?	☐	☐	☐	☐
How satisfied are you with the width of your scar?	☐	☐	☐	☐
How satisfied are you with the height of your scar compared to surrounding skin?	☐	☐	☐	☐
How satisfied are you with the texture of your scar (the way it feels to touch)?	☐	☐	☐	☐
How satisfied are you with the 'lumpiness' of your scar?	☐	☐	☐	☐
How satisfied are you with the 'shininess' of your scar?	☐	☐	☐	☐
Overall, how satisfied are you with the appearance of your scar?	☐	☐	☐	☐

APPENDIX 6. SUMMARY OF CHANGES FROM VERSION 2 TO VERSION 3

Formatting, consistency and minor editorial changes are not listed.

Protocol Section	Removed text is strikethrough and added text is **bold**	**Issue/rationale for change**
1 Synopsis	Name of Active Ingredient: StrataGraft~~,~~ **is** a viable~~, bioengineered,~~ **and metabolically active allogeneic** ~~cellularized scaffold product composed of a differentiated epidermal compartment comprised of epidermal cells from a single~~ **human** ~~donor grown on~~ **NIKS keratinocytes and human** dermal ~~equivalent composed of purified Type I animal collagen containing normal human~~ **fibroblasts** ~~from a second donor~~ **cellularized layered scaffold.**	Align language with NDC 736-200
Page 4	Version ~~2~~ **3** includes changes ~~to the Secondary Endpoints, Statistics and Safety Sections, as outlined in~~ **related to modifications in the xenotransplantation product requirements and prohibitions, which are reflected in Sections 4.4 and 11.9.1.5. Administrative issues and clarifications show changes in Section 1 (Synopsis) and Sections 6.1, 6.8, 8.2, 9.3, and 11. Appendix 6 is** a table of the summary of changes.	Outlines the changes made in this version the protocol

Protocol Section	Removed text is strikethrough and added text is **bold**	Issue/rationale for change
Section 4.4	~~The US FDA considers~~ StrataGraft ~~to be~~ **is a** xenotransplantation product because~~ of an historic exposure of the epidermal cells to well characterized mouse cells. Mouse cells are no longer used in the manufacture~~ **in the past, one of the cell types used to make StrataGraft was grown with mouse cells.** The cell banks have been ~~thoroughly~~ tested and found to be free of detectable ~~adventitious~~ **infectious** agents~~, and there have been no reported zoonotic infection in clinical trials.~~ **and mouse cells are no longer used in the manufacture of StrataGraft. There have been no identified health concerns associated with these mouse cells.** ~~However, the is a very low possibility that zoonotic infection could occur. It is important that patients/parents/legal guardians be made aware that people who receive treatment with StrataGraft should not donate blood, blood components, plasma, leukocytes, tissues, breast milk, ova, sperm or body parts for transplantation~~**.** **Recipients of xenotransplantation products are generally not eligible, per federal regulations, to donate whole blood, blood components, source plasma or source leukocytes. However, individual blood banks may request an exception from FDA. StrataGraft recipients wishing to donate blood or blood products should check with their donation center. StrataGraft recipients who otherwise meet the donor requirements are eligible to donate human cells, tissues, breast milk, ova, sperm, or body parts for transplantation.** A small amount of blood (3mL), called an archival sample, will be collected before StrataGraft application. This sample could be used as a baseline to assess health issues that may be related to treatment. These samples will be used only for the purpose of responding to a request from ~~the~~ FDA. Both archival samples and any associated ~~patient~~ **subject** information will be stored and used only as required and allowed by law. ~~Finally, although not required, in the event of a recipient's death, an autopsy should be considered.~~	Reflects modifications of the xenotransplantation product prohibitions/requirements for StrataGraft as granted by the US FDA

Protocol Section	Removed text is strikethrough and added text is **bold**	**Issue/rationale for change**
Section 6.1	Subjects will undergo baseline assessments including a targeted physical examination and collection of clinical laboratory assessments during Screening. After enrollment and StrataGraft application, wound assessments, photographs, and solicitation of AEs will be performed at each study visit via telephone or video interaction if the subject is unable to attend the visit. **However, wound closure may only be assessed at face-to-face visits.** If not collected during Screening, clinical laboratory samples will be collected via venipuncture performed prior to StrataGraft application on Day 1. Immunological samples (monitoring of PRA and anti-BSA antibodies) will be collected prior to StrataGraft application, and again between Week ~~7~~**6** and Month 6 for all treated subjects.	Wound closure may not be assessed via telephone or video interaction. Amended the Immunologic sample collection timing to match the timing outlined in the Schedule of Events.
Section 6.8, Table 2	Wound closure assessment line added to the Schedule of Events table with appropriate annotations	Clarify when wound closure observations are to be made

Protocol Section	Removed text is strikethrough and added text is **bold**	Issue/rationale for change
Section 6.8, Table 2	[d] Safety laboratory results will be **collected prior to StrataGraft application and** abstracted from the medical record**,** if available. If such results are not available, blood samples for study purposes will be collected as part of a clinically necessary venipuncture. **A second safety laboratory assessment will be performed between Study Day 28 and Study Week 11, with results abstracted from the medical record, if available, or collected as part of a clinically necessary venipuncture.** [e] During the excision/debridement procedure, photographs will be taken of the study site(s) 1) pre-excision/debridement, 2) post-excision/debridement, and 3) post-StrataGraft application. [f] Photograph all study treatment site(s) until complete closure, Week 12, or until the study burn is autografted; then photograph at Months 6 and 12. Photographs may be taken by trained caregivers or by study site personnel. [g] Conducted at the first observation of closure, Week 12 (if closed prior), and Months 6 and 12. [h] Immunological samples (monitoring of PRA and anti-BSA antibodies) will be collected prior to StrataGraft application and **one time** again between Week 6 and Month 6 for all treated subjects. [i] Archival blood samples will be collected before application of StrataGraft **and shipped for long-term storage**. [j] **Wounds will be assessed for percent re-epithelialization at least weekly, beginning at the Day 7 visit, until complete wound closure is confirmed.** Confirmation of closure will occur at least 2 weeks after initial observation of wound closure but no later than Week 20. **Maintenance of closure will be assessed at each subsequent study visit following confirmation of wound closure**. [k] Assess pain only if wound is open [l] Note reason(s) for continued hospitalization such as pain management, fluid or nutritional status, infection risk, ongoing infection, inability to perform activities of daily living, insufficient social support or other issues ~~[n] Treatment site evaluations include assessment for signs & symptoms of infection, percent re-epithelialization, closure and/or persistence of closure and application of autograft.~~ [m] Start/stop date, dose, unit, frequency, route, and indication for all prior (taken within 14 days prior to Day 1) and concomitant medications (taken from Screening through the Month 12 end of study visit) and nondrug therapies (eg. blood transfusions, oxygen supplementation, physical therapy, etc) administered will be recorded. **[n] Treatment site evaluations include assessment for signs & symptoms of infection or other adverse events and application of autograft.** ~~[o]~~[p] Medical history to include significant past morbidities, surgical procedures, etc. Limited physical exam will include review of systems and assessment of burn area, depth and location(s). ~~[q] Assess percent closure at least weekly until first observation of complete closure. Complete wound closure will be confirmed at a second visit at least 2 weeks after initial observation of closure but no later the Week 20.~~	Clarifications regarding footnotes to Table 2. Reordered alphabetically

Protocol Section	Removed text is strikethrough and added text is **bold**	Issue/rationale for change
Sections 8.1.2 and 8.2	(Section 8.1.2) ~~At investigator discretion, treatment of infected/suspected infected wound sites may include the use of targeted wound cleansing agents, topical antimicrobial agents (excluding silver-containing treatments), and/or systemic antibiotics.~~ (Section 8.2) The start and stop date, dose, unit, frequency, route of administration, and indication for all prior (taken within the 14 days prior to Day 1) and concomitant medications (taken from Screening through the Month 12 end of study visit) will be recorded. Start and stop dates of non-drug therapies (eg, oxygen supplementation, physical therapy, etc.) administered. Dates of transfusion of transfusions of blood or blood components as well as the number of units transfused will be recorded. **At investigator discretion, treatment of infected/suspected infected wound sites may include the use of targeted wound cleansing agents, topical antimicrobial agents and/or systemic antibiotics. Study wound sites may not be treated with any prohibited therapies, as outlined in Section 8.2.2.**	Migrated specific instructions related to treatment of infections to the section on concomitant medications/therapies. Linked to section on prohibited therapies.
Section 9.3	StrataGraft will be shipped to the study site on dry ice. Upon arrival at the site, ~~the~~ StrataGraft **may be maintained in the sealed shipping container until the date and time indicated on this container. If** StrataGraft will **not be used until after the date and time indicated on the shipping container, upon arrival at the site, StrataGraft should** be transferred from the shipping container to a secure, ultra-cold **(-70°C to -90°C)** freezer with monitored temperature. Details regarding shipment and storage requirements **can** ~~may~~ be found in the Manual of Procedures. Once StrataGraft has been ~~transferred into a site's ultra-cold freezer~~ **received at the site,** any excursion from required storage range (-70°C to -90°C) must be reported to the Sponsor as soon as the temperature fluctuation becomes known and prior to clinical use**.**	Clarification of acceptable product storage
Section 11	All study assessments and times are listed in the Schedule of Study Events (Section 6.8). General instructions for the administration of these assessments are provided in the following subsections. Additional (Unscheduled) safety assessments may be performed as needed. Specific instructions and questionnaires/forms (Where appropriate) will be provided in a study manual. All assessments will be recorded in the electronic case report form (eCRF). **It is expected the subjects will attend all scheduled study visits. Should a subject be unable to participate in an in-person visit, wound assessments and solicitation of AEs may be performed by telemedicine/video interactions. However, no assessment of wound re-epithelialization nor observation or confirmation of closure may be performed via video/telemedicine visits. These wound assessments may be performed only during a face-to-face visit.**	Clarification that only certain activities may be performed via telephone or video conferencing.

Protocol Section	Removed text is strikethrough and added text is **bold**	**Issue/rationale for change**
Section 11.9.1.5	An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the sponsor can be appropriate. AESI will be reported using the SAE/AESI Report Form and observe the same reporting timeline (Table 6). For this study, Adverse Events of Special Interest (AESI) include: • Signs/symptoms of endotoxin reaction (ie, combination of hypo/hyperpyrexia, hypo/hypertension tachycardia, tachypnea and change in mental status) within 24 hours after StrataGraft application • Unexpected or unusual infections • Dermatological malignancy • ~~Other transplantation related adverse events or clinical events that are suspicious of a xenogeneic cause, e.g. disease/disorder of known zoonotic origins~~	Reflects modifications of the xenotransplantation product requirements for StrataGraft as granted by the US FDA.